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FOR

HETEROCYCLIC SUBSTITUTED 2-METHYL-BENZIMIDAZOLE
ANTIVIRAL AGENTS

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HETEROCYCLIC SUBSTITUTED 2-METHYL-BENZIMIDAZOLE
ANTIVIRAL AGENTS

BACKGROUND OF THE INVENTION

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1. **Field of the Invention**

The present invention concerns antiviral compounds, their methods of preparation and their compositions, and use in the treatment of viral infections.
10 More particularly, the invention provides heterocyclic substituted 2-methylbenzimidazole derivatives for the treatment of respiratory syncytial virus infection.

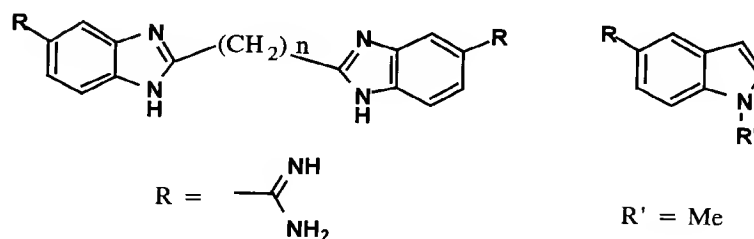
15 2. **Background Art**

Respiratory syncytial virus (RSV) is the leading cause of serious lower respiratory tract infection in infants, children, elderly and immunocompromised persons. A severe viral infection may result in bronchiolitis or pneumonia which may require hospitalization or result in death. (*JAMA*, 1997, 277, 12). Currently
20 only Ribavirin is approved for the treatment of this viral infection. Ribavirin is a nucleoside analogue which is administered intranasally as an aerosol. The agent is quite toxic, and its efficacy has remained controversial. RespiGam, approved for prophylaxis in high risk pediatric patients, is an intravenous immunoglobulin which effectively neutralizes the virus. Recently, Synagis, a monoclonal
25 antibody administered through intramuscular injection has also been approved for use in high risk pediatric patients. However, both drugs are very expensive. Accordingly, inexpensive, safe and effective antiviral agents against respiratory syncytial virus will be beneficial for patients.

30 Many agents are known to inhibit respiratory syncytial virus (De Clercq, *Int. J. Antiviral Agents*, 1996, 7, 193). Y. Tao et al. (EP 0 058 146 A1, 1998) disclosed that Ceterizine, a known antihistamine, exhibited anti-RSV

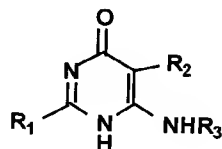
activity. Tidwell et al., *J. Med. Chem.* 1983, 26, 294 (US Patent 4,324,794, 1982), and Dubovi et al., *Antimicrobial Agents and Chemotherapy*, 1981, 19, 649, reported a series of amidino compounds with the formula shown below as inhibitors of RSV.

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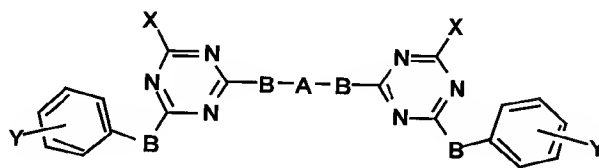
Hsu et al., US Patent 5,256,668 (1993) also disclosed a series of 6-aminopyrimidones that possess anti-viral activity against RSV.

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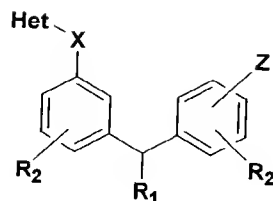
Y. Gluzman, et al., (AU Patent, Au-A-14,704, 1997) and P. R. Wyde et al. (*Antiviral Res.* 1998, 38, 31) disclosed a series of triazine containing compounds that were useful for the treatment and/or prevention of RSV infection.

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In addition, T. Nitz, et al., (WO Patent, WO 00/38508, 1999) disclosed a series of triaryl containing compounds that were useful for the treatment and/or prevention of RSV and related pneumoviral infections.

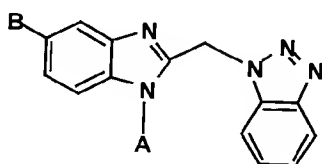
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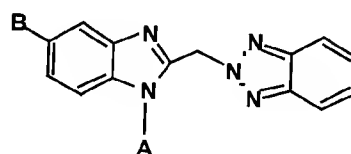
Moreover, Yu et al. (WO 020004900) also disclosed a series of substituted benzimidazoles that is useful for the treatment and prevention of RSV infection.



A related series of compounds were first disclosed by F. Pagani and F. Sparatore in *Boll Chim Farm.* 1965, 104, 427 and by G. Paglietti, et al. in *Il Farmaco, Ed. Sci.* 1975, 30, 505, and found to possess analgesic and anti-arrhythmic activity. The structural formula for these compounds are depicted in Formula Ia and Ib.

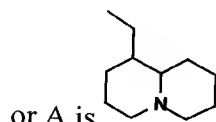


Formula Ia



Formula Ib

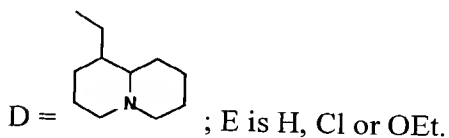
In Formula Ia and Ib, A is $-(CH_2)_n-N(R)_2$, $n = 2$ or 3 , $R = Me$ or Et ,



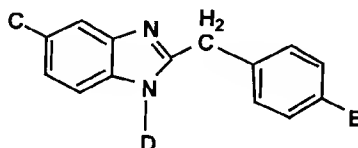
or A is ; $B = H, Cl, CF_3, CH_3CO, NO_2$.

Another series of closely related compounds that Sparatore had disclosed were in *Il Farmaco Ed. Sci.* 1967, 23, 344 (US patent 3,394, 141, 1968). Some

of the compounds were reported to have analgesic, anti-inflammatory or anti-pyretic activities. The structure of these compounds is depicted in Formula Ic. In Formula Ic, C = H, CF₃, or NO₂. D is -(CH₂)_n-NR₂, n = 2 or 3, R = Me or Et, or



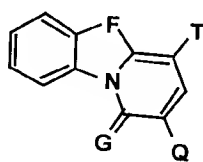
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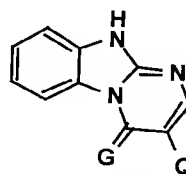
Formula Ic

Another series of compounds structurally related to this invention are pyrido[1,2-a]benzoxazoles and pyrimidio[1,2a]benzimidazoles disclosed by S. Shigeta et al in *Antiviral Chem. & Chemother.* 1992, 3, 171. These compounds have demonstrated inhibition of orthomyxovirus and paramyxovirus replication in HeLa cells. The structures of these compounds are shown in Formulas Id and Ie, in which F = NH, S, or O; Q = -NHCOPh, -COOH, COOEt, or CN; T = COMe, CN, or COOEt; G = O or NH.

15



Formula Id

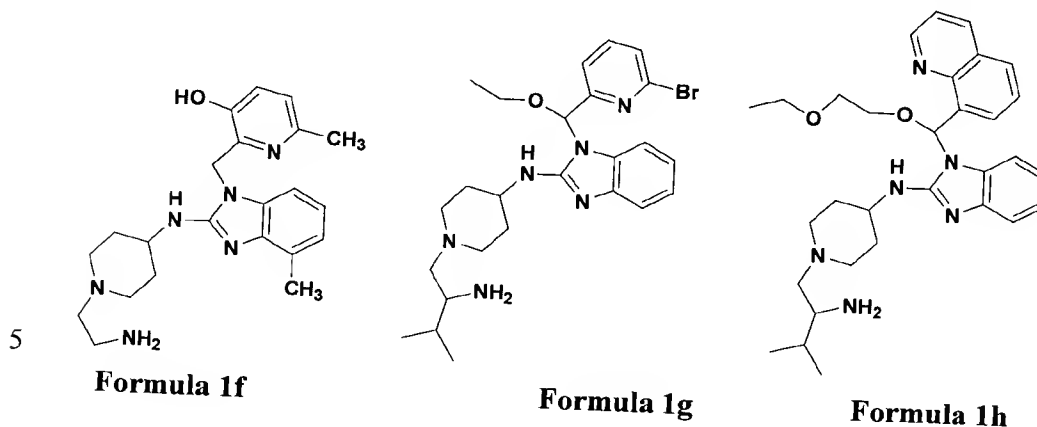


Formula Ie

A bis-benzimidazole with an ethylenediol linker shown below has also been reported as a potent inhibitor of rhinoviruses (Roderick, et al. *J. Med. Chem.* 1972, 15, 655).

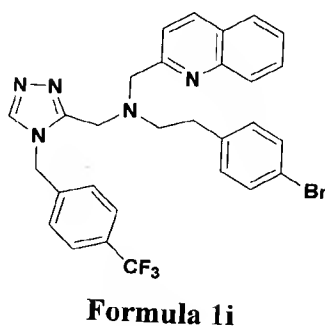
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A series of 2-aminobenzimidazoles have been reported by E. Janssens, et al. as inhibitors of RSV in a series of recent publications and representative examples formula 1f-1h are shown below from PCT WO 01/00611 A1; PCT WO 01/00612 and PCT WO 01/00615, respectively all published on January 4, 2001.

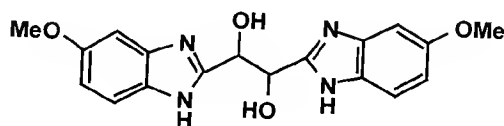


A series of triazole containing compounds have been reported by Janssen as inhibitors of RSV in PCT WO 01/36395 (May 25, 2001) and a representative example is shown below.

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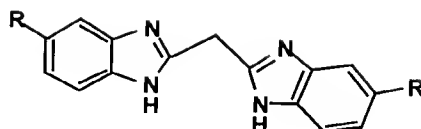


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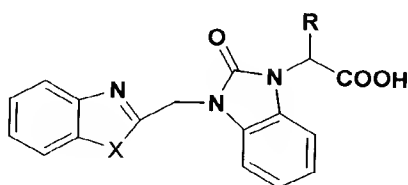


Other structurally related compounds are bis-benzimidazoles which possess antifungal activity (B. Cakir, et al. *Eczacilik Fak. Derg.* 1988, 5, 71).

6

R = H, NO₂

Also, H. R. Howard et al. reported a series of benzimidazolone-1-acetic acids that possessed aldolase reductase inhibitory activity (*Eur. J. Med. Chem.* 1992, 27, 779-789).



X = O, S

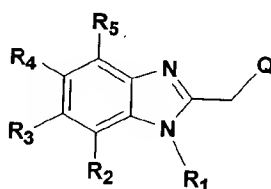
Other prior art related to the chemical structure of the present invention:

- (1) F. Sparatore, et al, "Derivati Benzotriazolici Attivi Sull'accrescimento Delle Piante," *Il Farmaco Ed. Sci.* 1978, 33, 901.
- (2) Katritzky, A. R. et al, "Synthesis and Transformations Of Substituted Benzazolyl- and Tetrazolyl(benzotriazol-1-yl)methanes," *J. Heterocyclic Chem.* 1996, 33, 1107.
- (3) Terri A. Fairley, et al. "Structure, DNA Minor Groove Binding, And Base Pair Specificity of Alkyl and Aryl-Linked Bis(amidinobenzimidazoles) and Bis(amidinoindoles), *J. Med. Chem.* 1993, 36, 1746.
- (4) R. K. Upadhyay et al, "New Synthesis and Biological Evaluation," *Indian J. Heterocyclic Chem.* 1994, 4, 121.

- (5) A. R. Katritzky, et al, "A New Route to N-substituted Heterocycles," *Tetrahedron*, 1993, 49, 2829.
- (6) K. Yu et al. in Substituted Benzimidazole Anti-viral Agents, PCT
5 WO00/04900 published February 3, 2000.

SUMMARY OF THE INVENTION

This invention relates to novel heterocyclic substituted 2-
10 methylbenzimidazoles and the antiviral activity against RSV. The structural
formula for these compounds are depicted in Formula I, and includes
pharmaceutically acceptable salts thereof,



15
Formula I

wherein:

R₁ is -(CR^aR^b)_n-X;

20 R^a, R^b are each independently selected from the group consisting of H, C₁₋₆ alkyl;
each of said C₁₋₆ alkyl being optionally substituted with one to six same or
different halogen;

25 X is H or C₁₋₆ alkyl; said C₁₋₆ alkyl being optionally substituted with a member
selected from the group consisting of (1) one to six same or different halogen or
hydroxy, (2) heteroaryl, (3) non-aromatic heterocyclic ring and (4) a member
selected from Group A;

Group A is a member selected from the group consisting of halogen, CN, OR^x, N^rR^cR^dR^e[T], NR^cR^d, COR^c, CO₂R^x, CONR^xR^y and S(O)_mR^c;

- 5 R^x and R^y are independently H or C₁₋₆ alkyl;
R^c, R^d and R^e are independently C₁₋₆ alkyl;

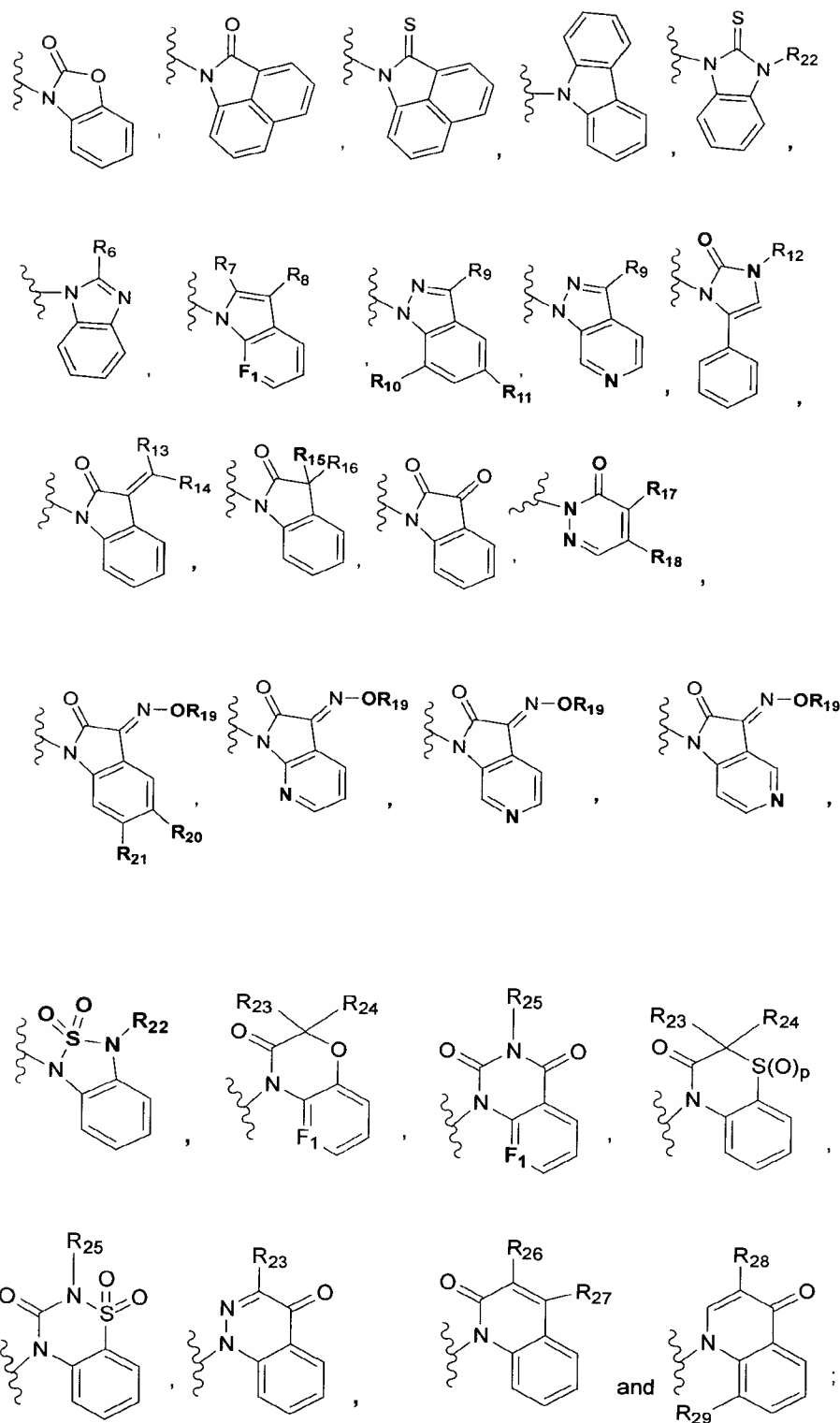
10 T⁻ is halogen, CF₃SO₃⁻ or CH₃SO₃⁻;

R₂ and R₅ are independently halogen or H;

- 15 R₃ and R₄ are each independently selected from the group consisting of H, halogen and C₁₋₆ alkyl; said C₁₋₆ alkyl can be optionally substituted with one to six same or different halogen;

Q is a member selected from the group consisting of

[illegible]



F₁ is CH or N;

R_6 is selected from the group consisting of H, halogen, NR^fR^g , SR^n and a five-membered heteroaryl containing one to two of the same or different heteroatoms selected from the group consisting of O, S and N;

- 5 R^f and R^g are independently H, C_{1-6} alkyl or C_{1-6} alkyl; said C_{1-6} alkyl optionally substituted with OR^h or CO_2R^h ;

R^h and R^i are independently H or C_{1-6} alkyl;

- 10 R^n is C_{1-6} alkyl optionally substituted with CO_2R^h ;

R_7 is H, or CO_2R^h ;

- 15 R_8 is H, COR^h , CO_2R^h or C_{1-6} alkyl; said C_{1-6} alkyl optionally substituted with OR^h ;

- 20 R_9 is H, halogen, heteroaryl, phenyl, phenyl substituted with a halogen group, phenyl substituted with a methanesulfonyl group, COR^h , CO_2R^h , C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-4} alkynyl; said C_{2-4} alkynyl optionally substituted with C_{1-6} cycloalkyl;

R_{10} and R_{11} are independently H, NO_2 or NR^hR^i

- 25 R_{12} is H, CO_2R^h or C_{1-2} alkyl; said C_{1-2} alkyl optionally substituted with phenyl;

R_{13} and R_{14} are independently selected from the group consisting of H, OR^h , $CONR^jR^k$, NR^lR^m and pyrrolidine; wherein said pyrrolidine is attached at the nitrogen atom;

- 30 R^j and R^k are independently H or C_{1-6} alkyl optionally substituted with phenyl;

R^l and R^m are independently C_{1-6} alkyl;

R₁₅ and R₁₆ are independently selected from the group consisting of H, OR^h, phenyl, pyridyl and C₁₋₆ alkyl; said C₁₋₆ alkyl optionally substituted with CO₂R^h;

- 5 R₁₇ and R₁₈ are independently selected from the group consisting of halogen, NR^lR^m, SR^h and morpholine; wherein said morpholine is attached at the nitrogen atom;

- 10 R₁₉ is selected from the group consisting of H, phenyl, C₂₋₆ alkenyl and C₁₋₆ alkyl; said C₁₋₆ alkyl optionally substituted with one to six same or different halogen, CO₂R^h, CONR^hRⁱ, pyridyl and one to three phenyl groups; wherein in the case of C₁₋₆ alkyl substituted with one phenyl group, said phenyl group is optionally substituted with a member selected from the group consisting of halogen, PO(OR^h)₂, CO₂R^h, SO₂Rⁿ and CONR^hRⁱ;

15

Rⁿ is C₁₋₆ alkyl;

R₂₀ and R₂₁ are independently H or halogen;

- 20 R₂₂ is C₁₋₆ alkyl;

R₂₃ and R₂₄ are independently H or C₁₋₆ alkyl;

- 25 R₂₅ is C₁₋₆ cycloalkyl or C₁₋₆ alkyl; said C₁₋₆ alkyl group optionally substituted with a member selected from the group consisting of CO₂R^h, PhCO₂R^h and one to six same or different halogens;

- 30 R₂₆ is selected from the group consisting of H, halogen, C₁₋₆ alkyl; C₂₋₆ alkenyl, OR^h and COR^h; said C₂₋₆ alkenyl being optionally substituted with OR^h;

R₂₇ is H, OR^h or CO₂R^h;

R_{28} is CO_2R^h ;

R_{29} is H or halogen;

5 heteroaryl is a 5- or 6-membered aromatic ring containing at least one and up to four non-carbon atoms selected from the group consisting of O, N and S;

non-aromatic heterocyclic ring is a 3 to 7-membered non-aromatic ring
containing at least one and up to four non-carbon atoms selected from the group
10 consisting of O, N and S; and

p is 0-2.

15 In a preferred embodiment, heteroaryl is selected from the group consisting of pyridyl, thiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,4-oxadiazol-5-one and tetrazole.

In another preferred embodiment, non-aromatic heterocyclic ring is
selected from the group consisting of pyrrolidine and piperidine.
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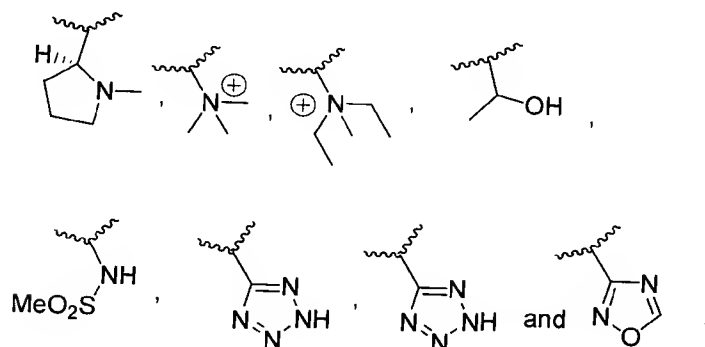
R^a and R^b are hydrogen.

In another preferred embodiment, R_1 is $-(\text{CH}_2)_n\text{-X}$ and n is 2-4.

25 In another preferred embodiment, R_3 and R_4 are each independently selected from the group consisting of H, fluorine and C_{1-2} alkyl; said C_{1-2} alkyl being optionally substituted with one to three fluorine atoms.

In another preferred embodiment R_1 is 3-methyl-2-butyl or $-(\text{CH}_2)_n\text{-X}$
30 wherein n is 2-4;

X is a member selected from the group consisting of
 -F, -CN, -SR^c, -SO₂R^c, -OR^x, -COR^c, CO₂R^x, CONR^xR^y,
 [NR^cR^dR^e][T⁻],



R^c, R^d and R^e are independently C₁₋₄ alkyl; and

R^x and R^y are independently H or C₁₋₄ alkyl.

In another preferred embodiment, R₂ and R₅ are independently H.

Another preferred embodiment includes a pharmaceutical composition which comprises a therapeutically effective amount of one or more of the aforementioned compounds of Formula I, including pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

Another preferred embodiment includes method for treating mammals infected with RSV, and in need thereof, which comprises administering to said mammal a therapeutically effective amount of a compound of Formula I, including pharmaceutically acceptable salts thereof.

The term pharmaceutically acceptable salt includes solvates, hydrates, acid addition salts and quarternary salts. The acid addition salts are formed from a compound of Formula I and a pharmaceutically acceptable inorganic acid including but not limited to hydrochloric, hydrobromic, sulfuric, phosphoric,

methanesulfonic, acetic, citric, malonic, fumaric, maleic, sulfamic, or tartaric acids. Quaternary salts include chloride, bromide, iodide, sulfate, phosphate, methansulfonate, citrate, acetate, malonate, fumarate, sulfamate, and tartrate.

5 Halogen means bromine, chlorine, iodine and fluorine.

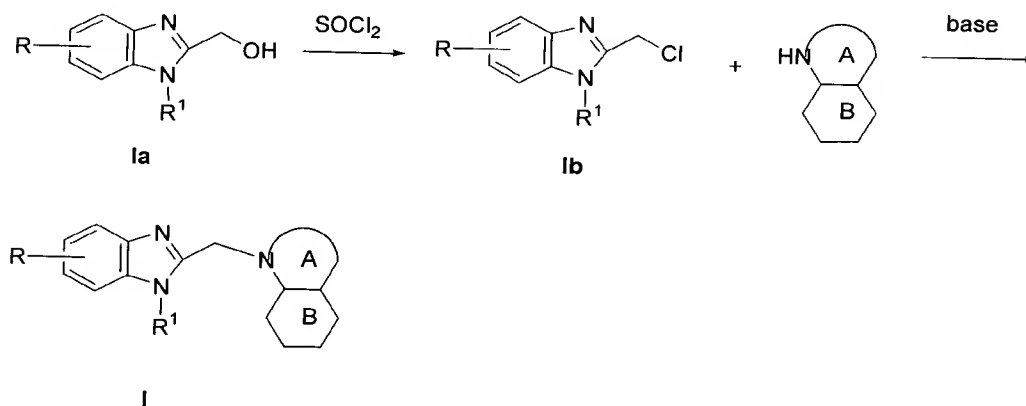
DETAILED DESCRIPTION OF THE INVENTION

10 Compounds of Formula I may be prepared using the procedures outlined in Schemes I-X.

Compounds of Formula I can be prepared as shown in Scheme I.

15 Treatment of substituted or unsubstituted 2-hydroxymethylbenzimidazole Ia with thionyl chloride provides 2-chloromethylbenzimidazole Ib. Coupling of chloride Ib with a heterocycle in the presence of base, preferred cesium carbonate, sodium hydride, or phosphazene base such as BTPP gives compounds of Formula I.

Scheme I



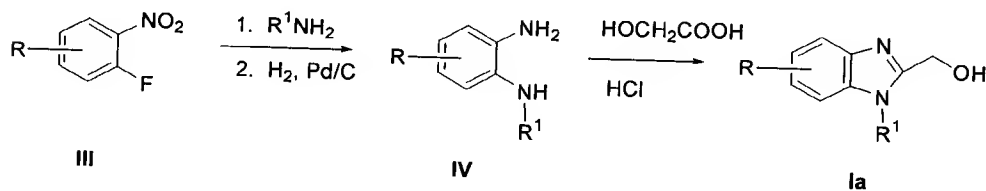
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The synthesis of compounds of Formula Ia is described in Schemes Ia and Ib. Coupling of substituted or unsubstituted 2-fluoro-nitrobenzene (III) with an appropriate amine followed by reduction under catalytic hydrogenation conditions gives diamines of Formula IV. Cyclization of diamine IV with

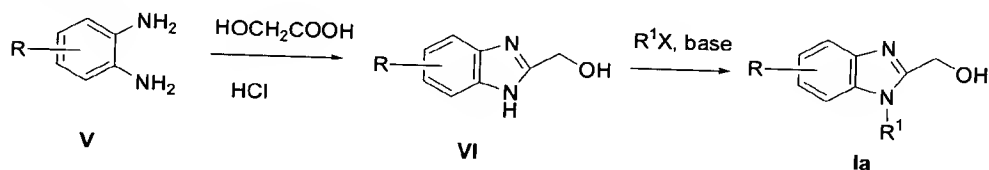
glycolic acid in 4-6 N HCl gives compounds of Formula Ia (Scheme Ia).

Alternatively, a diamine of Formula V can be cyclized with glycolic acid in 4-6 N HCl to give 2-hydroxymethyl benzimidazole VI which is treated with base preferably cesium carbonate or sodium hydride followed by the addition of an appropriate halide to give compound Ia (Scheme Ib).

Scheme Ia



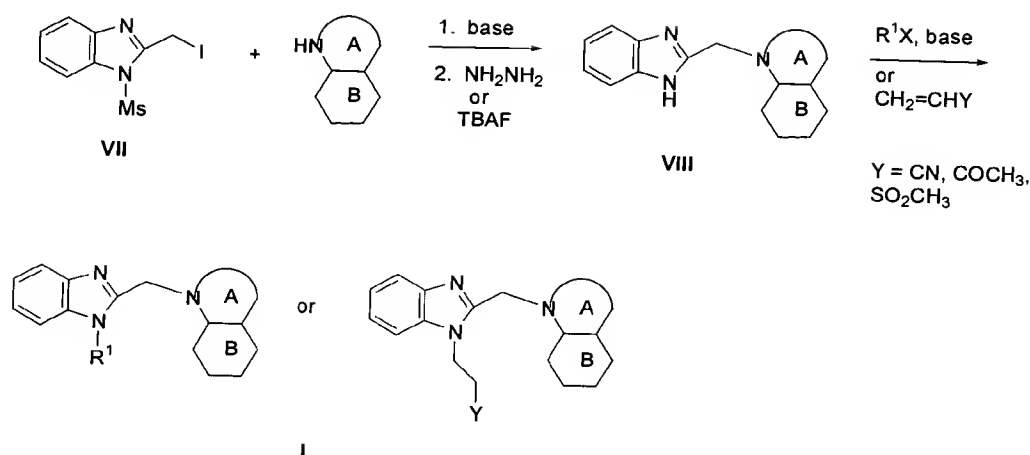
10 Scheme Ib



Compounds of Formula I can also be prepared as shown in Scheme II.

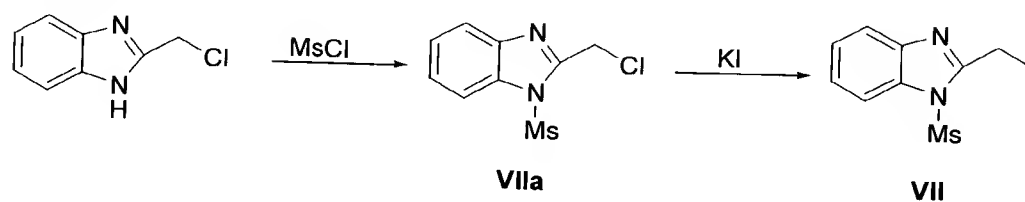
Coupling of the mesylate VII and an appropriate heterocycle in the presence of base such as sodium hydride or BTPP followed by cleavage of the mesylate with tetrabutylammonium fluoride or hydrazine gives intermediate VIII. Alkylation of compound VIII with an appropriate halide in the presence of base such as sodium hydride, BTPP or cesium carbonate gives compound of Formula I. Alternatively, compounds of Formula I can be obtained through a Michael addition of VIII with acrylonitrile, methyl vinyl ketone, or methyl vinyl sulfone.

Scheme II

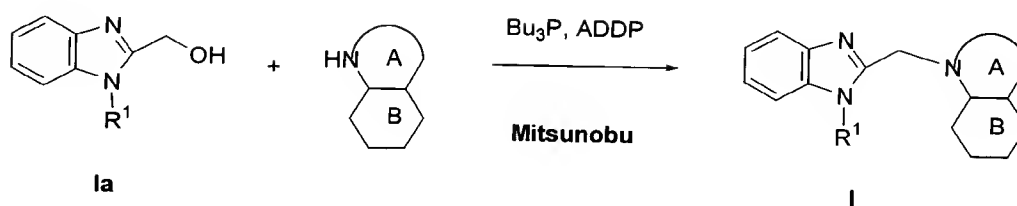


The compound VII can be prepared using the reaction sequence depicted in Scheme IIa. In Scheme IIa, 2-chloromethylbenzimidazole reacts with methanesulfonyl chloride (MsCl) and triethylamine to give compound of Formula VIIa. The chloride can be refluxed with potassium iodide in acetone to produce the compound of Formula VII, as described in PCT WO 00/04900.

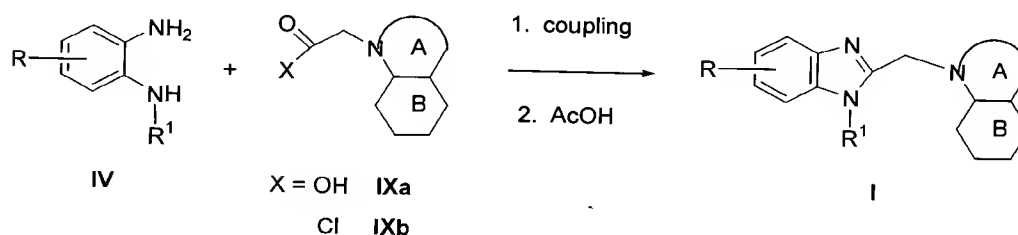
10 Scheme IIa



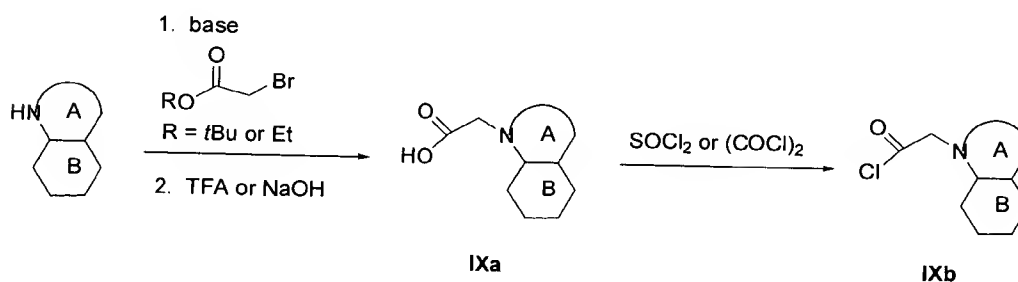
Alternatively, compounds of Formula I can be obtained through Mitsunobu coupling of Ia with an appropriate heterocycle in the presence of tributylphosphine and 1,1'-(azodicarbonyl)dipiperidine (ADDP) as depicted in Scheme III.

Scheme III

In a different approach, compounds of Formula I were prepared using the synthetic route illustrated in Scheme IV. The diamine IV is first coupled either with acid IXa through an amide coupling reagent such as EDAC and HOBT or 2-chloro-1-methyl pyridinium iodide or with acid chloride IXb in the presence of base. The crude intermediate is directly cyclized to the benzimidazole in refluxing acetic acid providing compounds of Formula I.

Scheme IV

Scheme IVa describes the synthesis of compounds of formulas IXa and IXb. An appropriate heterocycle is alkylated with either *t*-butyl bromoacetate or ethyl bromoacetate followed by hydrolysis of the ester with trifluoroacetic acid or sodium hydroxide gives acid IXa. Conversion of the acid to the acid chloride with thionyl chloride or oxalyl chloride provides a compound of Formula IXb.

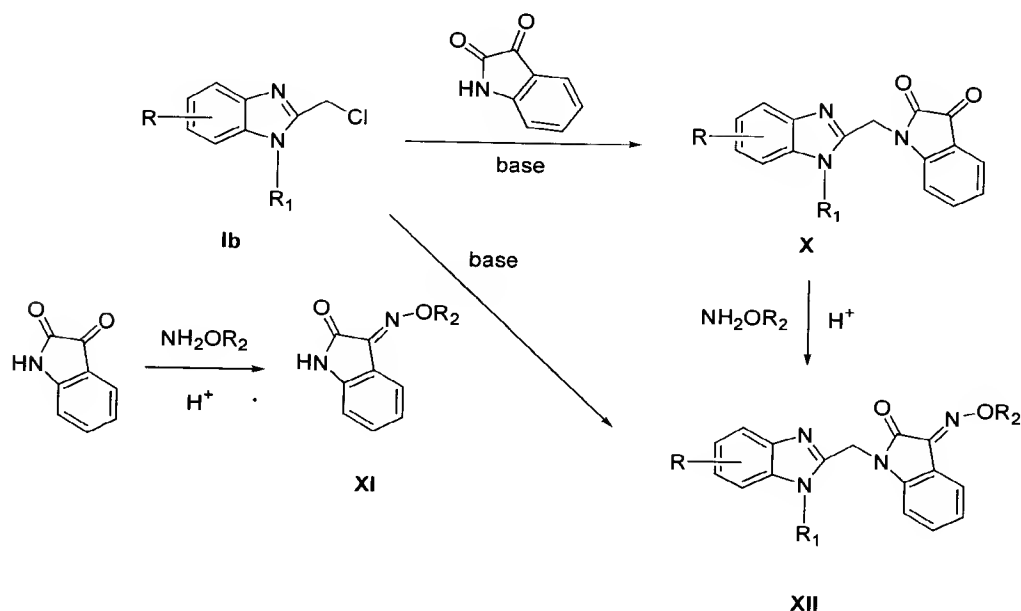
Scheme IVa

Some compounds of Formula I can be further derivatized with a specific example being the isatin and oxime series. Derivative compounds of Formula XII can be prepared as outlined in Schemes V, VI, and VII.

- 5 In Scheme V, chloride Ib reacts with isatin in the presence of a base, such as sodium hydride or BTPP, to give compounds of Formula X. The isatin derivative X and an appropriate hydroxylamine are refluxed with an acid catalyst to provide oximes of Formula XII. The chloride Ib also can react directly with an oxime of Formula XI to afford compounds of Formula XII.

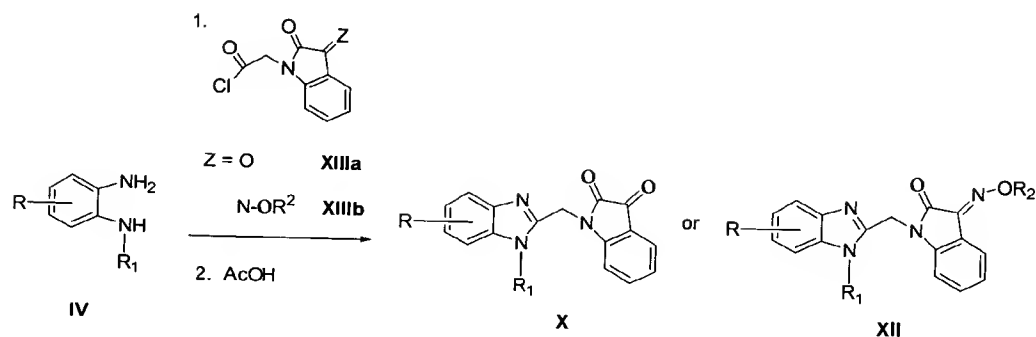
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Scheme V

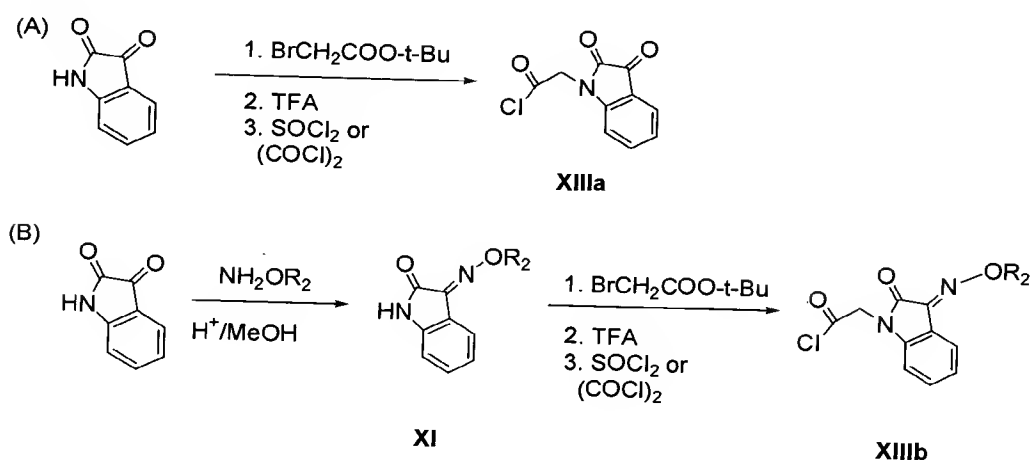


- Alternatively, phenylenediamine of Formula IV was coupled to an isatin or oxime acetyl chloride of Formula XIIIa or XIIIb, followed by ring closure in refluxing acetic acid to provide compounds of Formula X or XII (Scheme VI). The corresponding isatin or oxime acetyl chloride intermediates XIIIa or XIIIb were synthesized using standard procedures as shown in Scheme VIa.
- 15

Scheme VI



Scheme VIa

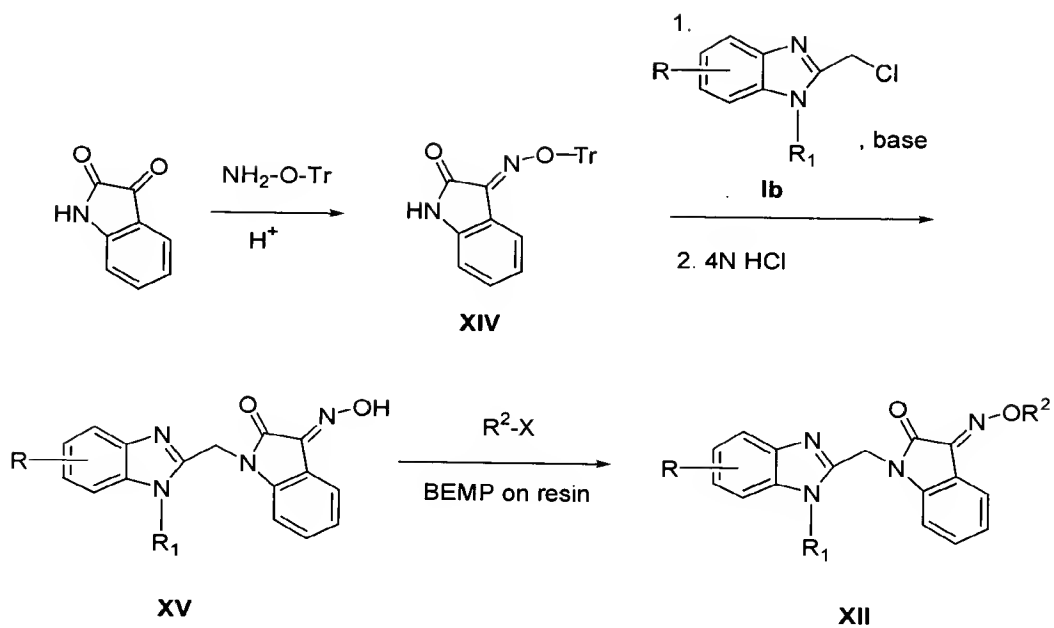


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In an alternative approach depicted in Scheme VII, isatin is refluxed with O-tritylhydroxylamine. The resulting oxime **XIV** is coupled to chloride **Ib** and subsequently hydrolyzed to give oxime derivative of Formula **XV**. Alkylation of the oxime with an appropriate halide in the presence of BEMP on polystyrene yields compounds of Formula **XII**.

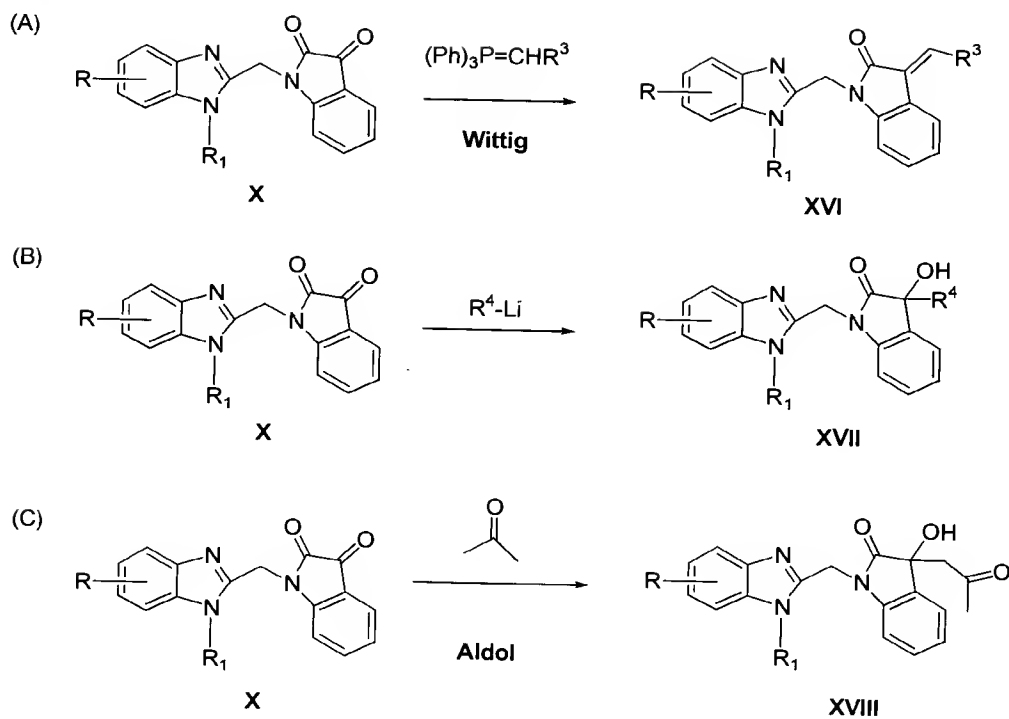
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Scheme VII

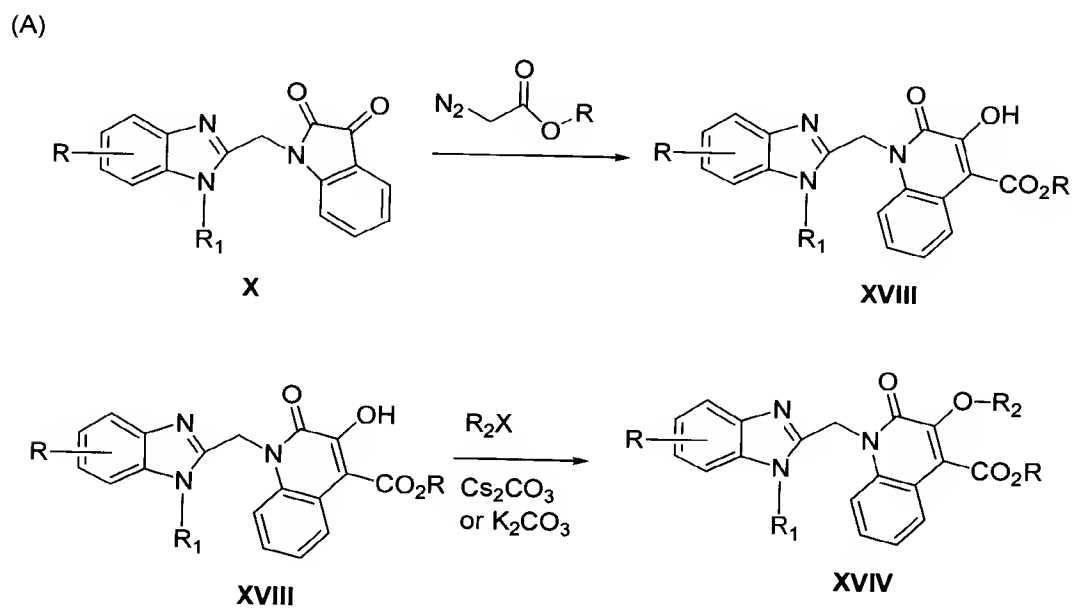


- 5 In addition to oxime derivatives, isatin compound X can be converted to derivatives XVI, XVII, and XVIII through Wittig reaction, reaction with organolithium reagent, or Aldol condensation as depicted in Scheme VIII.

Scheme VIII

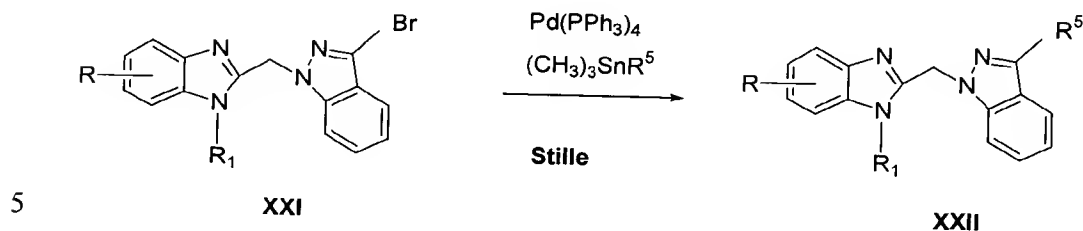


In addition, compounds of Formula X can be converted to 2-quinolone derivatives by reaction of the isatin X with ethyl diazoacetate to give derivative XIX.



Compound of Formula XXII, prepared according to Scheme I, II, III, or IV, can be further derivatized through Stille coupling as shown in Scheme IX.

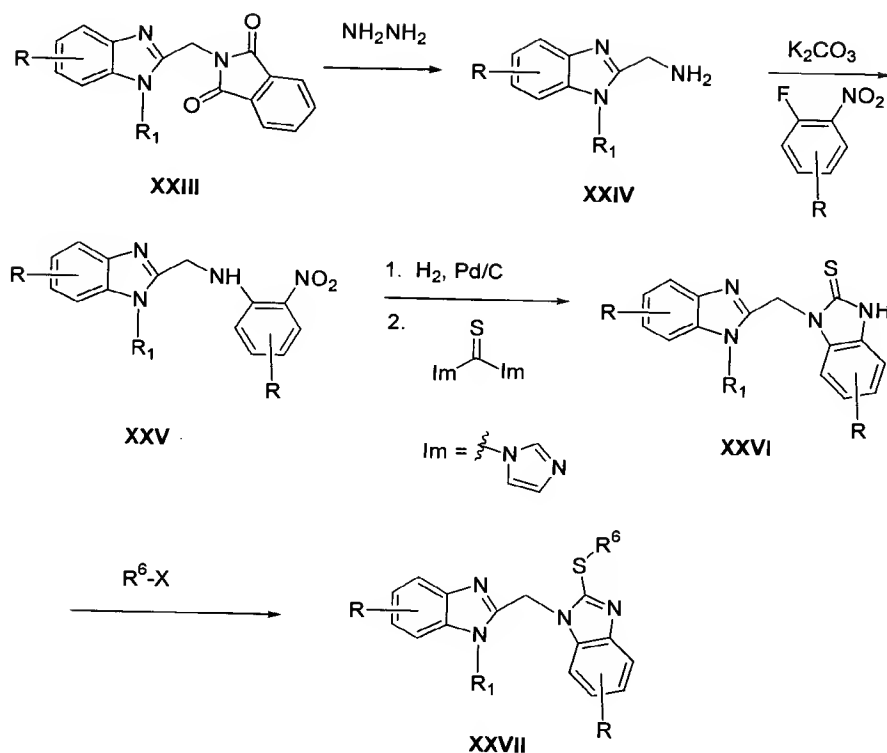
Scheme IX



Derivatives of Formula XXIV are prepared by formation of the heterocyclic ring as described in Scheme X. Compound XXIII, prepared according to Scheme I with phthalimide as the heterocycle, is treated with hydrazine to afford the amine XXIV which is coupled to a 2-fluoro-nitrobenzene. Reduction under catalytic hydrogenation conditions followed by cyclization with 1,1'-thiocarbonyldiimidazole provides compound of Formula XXVI which can be further derivatized by alkylation with an appropriate halide to compound XXVII.

10

Scheme X



Abbreviations used in Schemes I-X and experimental section:

- 5
- AcOH: glacial acetic acid
- BEMP: 2-*t*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine
- BTPP: *t*-butylimino-tri(pyrrolidino)phosphorane
- 10 DIEA: *N,N*-diisopropylethylamine
- DMF: dimethylformamide
- EDAC: 1-[3-(dimethyl amino)propyl]-3-ethylcarbodiimide hydrochloride
- EtOH: ethyl alcohol
- EtOAc: ethyl acetate
- 15 Et₂O: diethyl ether
- HOBT: 1-hydroxybenzotriazole hydrate
- MeOH: methyl alcohol
- Ph: phenyl

Prep HPLC: preparative high performance liquid chromatography

TFA: trifluoroacetic acid

THF: tetrahydrofuran.

Tr: trityl or triphenylmethyl

5 TBDMS: *t*-butyldimethylsilyl

TMS: trimethylsilyl

10 It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established infections or symptoms.

15 It will be further appreciated that the amount of a compound of the invention required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient, and will ultimately be at the discretion of the attendant physician or veterinarian. In general however, a suitable dose will be in the range of from about 0.01 to 750 mg/kg of body weight per day preferably in the range of 0.1 to 100 mg/kg/day, most preferably in the range of 0.5 to 25 mg/kg/day.

20 Treatment is preferably commenced before or at the time of infection and continued until virus is no longer present in the respiratory tract. However, the treatment can also be commenced when given post-infection, for example after the appearance of established symptoms.

25 Suitable treatment is given 1-4 times daily and continued for 3-7, e.g. 5 days post infection depending upon the particular compound used.

30 The desired dose may be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

The compound is conveniently administered in unit dosage form, for example, containing 10 to 1500 mg, conveniently 20 to 1000 mg, most conveniently 50 to 700 mg of active ingredient per unit dosage form.

5 While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation.

10 The invention thus further provides a pharmaceutical formulation comprising a compound of the Formula I, or a pharmaceutically acceptable salt or derivative thereof together with a pharmaceutically acceptable carrier thereof.

15 The carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

 The pharmaceutical formulations may be in the form of conventional formulations for the intended mode of administration.

20 For intranasal administration according to the method of the invention the compounds of the invention may be administered by any of the methods and formulations employed in the art for intranasal administration.

25 Thus in general the compounds may be administered in the form of a solution or a suspension or as a dry powder.

30 Solutions and suspensions will generally be aqueous, for example prepared from water alone (for example sterile or pyrogen-free water), or water and a physiologically acceptable co-solvent (for example ethanol, propylene glycol, and polyethylene glycols such as PEG 400).

 Such solutions or suspensions may additionally contain other excipients, for example, preservatives (such as benzalkonium chloride), solubilizing

agents/surfactants such as polysorbates (e.g. Tween 80, Span 80, benzalkonium chloride), buffering agents, isotonicity-adjusting agents (for example sodium chloride), absorption enhancers and viscosity enhancers. Suspensions may additionally contain suspending agents (for example microcrystalline cellulose, carboxymethyl cellulose sodium).

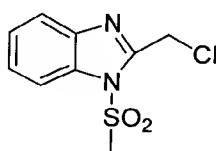
Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multidose form. In the latter case a means of dose metering is desirably provided. In the case of a dropper or pipette this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray this may be achieved for example by means of a metering atomizing spray pump.

Intranasal administration may also be achieved by means of an aerosol formulation in which the compound is provided in a pressurized pack with a suitable propellant such as a chlorofluorocarbon (CFC), for example dichlorodifluoromethane, trichlorofluoromethane or dichlorotetrafluoroethane, carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Experimental Section

Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Bruker Avance 500, AC-300, Bruker DPX-300 or a Varian Gemini 300 spectrometer. All spectra were determined in CDCl_3 , CD_3OD , d-acetone or DMSO-d_6 and chemical shifts are reported in δ units relative to tetramethylsilane (TMS). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; b, broad peak; dd, doublet of doublets; dt, doublet of triplets. Mass spectroscopy was performed on a Finnigan SSQ 7000 quadrupole mass spectrometer in both positive and negative electrospray ionization (ESI) modes or

on a LC-MS using Shimadzu LC-10AS with micromass platform LC single quadrupole mass spectrometer in positive electrospray ionization. High resolution mass spectroscopy was recorded using Finnigan MAT 900. Infrared (IR) spectra were recorded on a Perkin-Elmer system 2000 FT-IR. Elemental analysis was performed with Perkin-Elmer series II, model 2400 CHN/O/S analyzer. Column chromatography was performed on silica gel from VWR Scientific. Preparative HPLC was performed using Shimadzu LC-8A on a C18 column eluted with mixture of MeOH in water with 0.1 % trifluoroacetic acid.

**1a**

To a solution of 2-(chloromethyl)benzimidazole (80 g, 0.48 mol) and methanesulfonyl chloride (58.3 mL, 0.75 mol) in methylene chloride (0.5 L), triethylamine (136 mL, 0.97 mol) was added dropwise under nitrogen. The resulting mixture was stirred at room temperature for 6 hours. The mixture was filtered and the filtrate was evaporated. The residue was triturated in methanol and filtered to afford 74.9 g of compound **1a** as a brown solid:

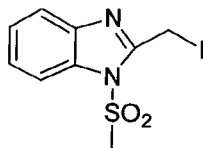
^1H NMR (CDCl_3) δ 3.44 (s, 3 H), 5.11 (s, 2 H), 7.40-7.49 (m, 2 H), 7.76-7.82 (m, 1 H), 7.85-7.91 (m, 1 H);

IR (KBr, cm^{-1}) 3027, 2920, 1371, 1349, 1177, 1144, 1059;

MS m/e 245 (MH^+);

Anal. Calcd for $\text{C}_9\text{H}_9\text{ClN}_2\text{O}_2\text{S}$: C, 44.18; H, 3.71; N, 11.45

Found: C, 44.09; H, 3.57; N, 11.49.

**1b**

A solution of potassium iodide (206 g, 1.24 mol) and compound **1a** (74.8 g, 0.414 mol) in acetone (1 L) was stirred at reflux under nitrogen for 4 hours. The solid was filtered and the filtrate was evaporated. The crude product was triturated in MeOH and filtered to give 83 g of compound **1b** as a solid:

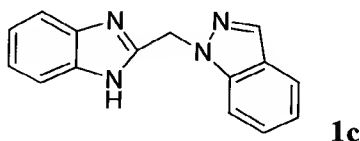
5

^1H NMR (CDCl_3) δ 3.48 (s, 3 H), 4.97 (s, 2 H), 7.40-7.50 (m, 2 H), 7.75-7.85 (m, 2 H);

IR (KBr, cm^{-1}) 3022, 2916, 1366, 1173, 1055, 966, 763, 745;

MS m/e 336 (MH^+);

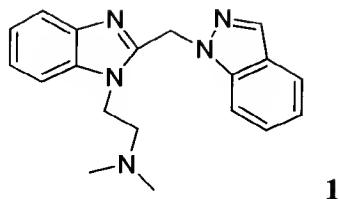
10 Anal. Calcd for $\text{C}_9\text{H}_9\text{IN}_2\text{O}_2\text{S}$: C, 32.16; H, 2.70; N, 8.33
 Found: C, 32.05; H, 2.63; N, 8.22.



15 To a solution of indazole (591 mg, 5.00 mmol) in DMF (7 mL) was added NaH (60% suspension in mineral oil, 200 mg, 5.00 mmol). After stirring for 30 minutes, compound **1b** (1.51 g, 4.50 mmol) was added and the resulting solution was stirred at room temperature overnight. The mixture was diluted with saturated aqueous NaHCO_3 , and extracted with Et_2O . The combined extracts
20 were dried over MgSO_4 and evaporated. Purification by flash column chromatography (gradient, EtOAc :hexanes = 1:4 to 2:1) gave an intermediate which was subsequently treated with hydrazine (2 mL) in MeOH (10 mL) and stirred at 65°C for 2 hours. The solvent was evaporated and the residue was purified by column chromatography (gradient, EtOAc :hexanes = 1:1 to straight
25 EtOAc to EtOAc :MeOH = 10:1). Recrystallization from EtOAc and hexanes gave 359mg (29% yield) of compound **1c**:

^1H NMR (CDCl_3) δ 5.88 (s, 2 H), 7.20 (t, $J = 4.5$ Hz, 1 H), 7.24-7.27 (m, 2 H), 7.41 (t, $J = 4.5$ Hz, 1 H), 7.55 (bs over d, $J = 5.2$ Hz, 2 H), 7.75 (d, $J = 4.9$ Hz, 1
30 H), 8.11 (s, 2 H);

MS m/e 249 (MH^+).



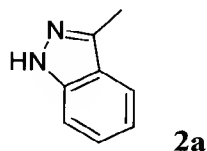
5 To a mixture of compound **1c** (248 mg, 1.00 mmol) and NaH (60% suspension in mineral oil, 96 mg, 2.40 mmol) in DMF (3 mL) was added 2-chloro-N,N-dimethylethylamine hydrochloride (158 mg, 1.10 mmol) and the mixture was stirred at 65°C for 4 hours. The reaction was quenched with saturated aqueous NaHCO_3 and extracted with Et_2O . The combined extracts were
10 dried over MgSO_4 and evaporated. The resulting residue was purified by flash column chromatography (gradient, $\text{EtOAc}:\text{hexanes} = 1:1$ to straight EtOAc to $\text{EtOAc}:\text{MeOH} = 10:1$) to give 27 mg (14% yield) of compound **1** as a light yellow gum:

15 ^1H NMR (CDCl_3) δ 2.24 (bs, 8 H), 4.29 (bt, $J = 6.8$ Hz, 2 H), 5.90 (s, 2 H), 7.07 (t, $J = 7.7$ Hz, 1 H), 7.19-7.29 (m, 4 H), 7.62 (t, $J = 7.6$ Hz, 2 H), 7.71-7.75 (m, 1 H), 7.96 (s, 1 H);

IR (KBr, cm^{-1}) 2944, 2772, 1616, 1464, 1418, 1333, 1164, 743;

MS m/e 320 (MH^+).

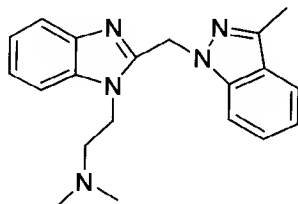
20



A mixture of 2'-bromoacetophenone (2.00 g, 10.05 mmol) and hydrazine (322 mg, 10.05 mmol) in EtOH (10 mL) was refluxed for 48 hours. The solvent
25 was evaporated. To the residue in THF (75 mL) was added 1 N HCl (15 mL). The resulting emulsion was warmed and stirred for 10 minutes. The mixture was

neutralized with saturated NaHCO_3 . The organic layer was dried over MgSO_4 and evaporated. The residue was subjected to column chromatography (EtOAc/hexanes , 1:1) to give 363 mg (27% yield) of compound **2a** which was used immediately upon isolation.

5

**2**

Compound **2** was prepared using the same procedure as compound **1** starting with compound **2a**:

10

^1H NMR (CDCl_3) δ 2.24 (bs, 8 H), 2.57 (s, 3 H), 4.35 (t, $J = 7.2$ Hz, 2 H), 5.86 (s, 2 H), 7.09 (dt, $J = 0.8, 7.9$ Hz, 1 H), 7.24-7.32 (m, 4 H), 7.56 (d, $J = 8.9$ Hz, 1 H), 7.61 (d, $J = 8.0$ Hz, 1 H), 7.77-7.81 (m, 1 H);

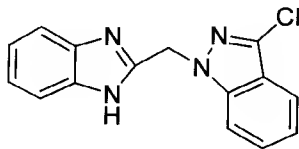
IR (KBr, cm^{-1}) 3406, 2824, 1615, 1508, 1456, 1351, 1332, 744;

15

MS m/e 334 (MH^+);

Anal. Calcd for $\text{C}_{20}\text{H}_{23}\text{N}_5 \cdot 0.25 \text{H}_2\text{O}$: C, 71.08; H, 7.01; N, 20.72

Found: C, 71.05; H, 7.06; N, 20.70.

**3a**

20

Compound **3a** was prepared using the same procedure as compound **1c** with 3-chloroindazole in 44% yield:

^1H NMR (CDCl_3) δ 5.79 (s, 2 H), 7.17-7.27 (m, 3 H), 7.40-7.60 (m, 1 H), 7.51-7.54 (m, 3 H), 7.66 (d, $J = 8.2$ Hz, 1 H);

25

IR (KBr, cm^{-1}) 2864, 2751, 1615, 1464, 1445, 1336, 1279, 1176, 989, 749.

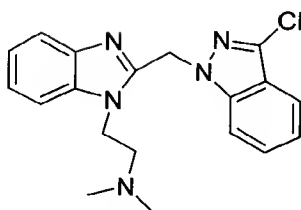
MS m/e 283 (MH⁺);

Anal. Calcd for C₁₅H₁₁ClN₄:

C, 63.72; H, 3.92; N, 19.82

Found:

C, 63.47; H, 3.98; N, 19.83.

**3**

Compound **3** was prepared using the same procedure as compound **1** in 63% yield:

¹H NMR (CD₃OD) δ 2.28 (s, 6 H), 2.34 (t, J = 7.0 Hz, 2 H), 4.38 (t, J = 7.0 Hz, 2 H), 5.88 (s, 2 H), 7.15-7.25 (m, 1 H), 7.26-7.40 (m, 3 H), 7.62-7.68 (m, 3 H), 7.76-7.80 (m, 1 H);

IR (KBr, cm⁻¹) 2945, 2825, 2773, 1616, 1496, 1466, 1336, 1253, 1172, 1006, 992, 746;

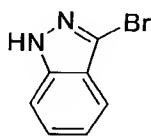
MS m/e 353 (MH⁺);

Anal. Calcd for C₁₉H₂₀ClN₅:

C, 64.49; H, 5.70; N, 19.79

Found:

C, 64.54; H, 5.72; N, 19.80.

**4a**

3-Bromoindazole **4a** was prepared using a procedure described by Boulton, B. E. and Coller, A. W (*Aust. J. Chem.*, **1974**, 27, 2343-2346):

A solution of bromine (0.99 g, 6.19 mmol) in 10% NaOH was slowly added to a suspension of indazole (1 g, 8.50 mmol) in 2 N NaOH (25 mL). The reaction mixture became a thick white slurry. After stirring for 2 hours, a small

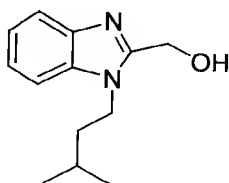
amount of sodium bisulfite was added and the solution was neutralized with 1 N HCl. The white solid was filtered and washed with water. Recrystallization from water gave 0.76 g (45% yield) of 3-bromoindazole **4a**:

¹H NMR (CDCl₃) δ 7.22-7.27 (m, 1 H), 7.43-7.52 (m, 2 H), 7.60-7.67 (m, 1 H); IR (KBr, cm⁻¹) 3154, 2944, 2915, 1624, 1479, 1331, 1242, 1026, 901, 770, 735, 639;

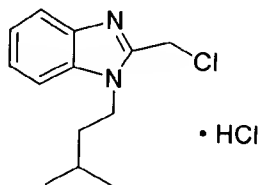
MS m/e 195 (MH⁺);

Anal. Calcd for C₇H₅BrN₂: C, 42.67; H, 2.56; N, 14.22

Found: C, 42.37; H, 2.55; N, 14.06.

**4b**

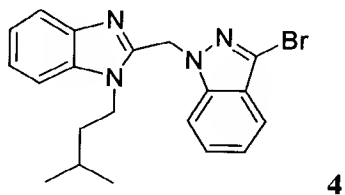
To a solution of 2-hydroxymethylbenzimidazole (27.1 g, 182.9 mmol) in a 1:1 mixture of DMF/THF (200 mL) was added NaH (60% in mineral oil, 8.05 g, 201.2 mmol) at room temperature. After stirring for 1.5 hour, 1-bromo-3-methylbutane (29 g, 192 mmol) was added and the mixture was stirred at 75 °C overnight. The mixture was adjusted to neutral pH with concentrated HCl and the solvent was evaporated. The residue was diluted with EtOAc, washed with water, dried over MgSO₄, and evaporated. The residue was crystallized from EtOAc/hexane to give 29 g of compound **4b** as white solid. The mother liquor was purified by flash chromatography (EtOAc:hexane = 1:1 to 2:1 and then EtOAc:MeOH = 10:0 to 10:1) to give additional 5.24 g (total 86% yield) of **4b**.

**4c**

To a solution of compound **4b** (34.24g, 156.9 mmol) in CH₂Cl₂ (100 mL) was slowly added SOCl₂ (28 g, 235.4 mmol) with ice-bath cooling. The resulting solution was stirred at room temperature for 1 hour and evaporated. The residue was dried *in vacuo* and then triturated with a mixture of CH₂Cl₂/Et₂O to give
5 41.25 g (96% yield) of compound **4c** as a white solid:

¹H NMR (DMSO-d₆) δ 0.99 (d, J = 6.3 Hz, 6 H), 1.72-1.79 (m, 3 H), 4.47-4.52 (m, 2 H), 5.36 (s, 2 H), 7.52-7.61 (m, 2 H), 7.82-7.92 (m, 2 H);
MS m/e 237 (MH⁺).

10



To a solution of 3-bromoindazole (**4a**, 303 mg, 1.54 mmol) in CH₃CN (15 mL) was added NaH (60% suspension in mineral oil, 68 mg, 1.69 mmol).
15 After stirring for 30 minutes at room temperature, compound **4c** was added and the reaction was stirred at room temperature for 22 hours. The reaction was quenched with saturated aqueous NaHCO₃ and extracted with Et₂O. The combined organic extracts were dried over MgSO₄ and evaporated. Purification of the resulting residue by column chromatography (hexanes / EtOAc, 1.5:1)
20 followed by trituration with hexanes gave 191 mg (31% yield) of compound **4**:

¹H NMR (CDCl₃) δ: 0.91 (d, J = 6.6 Hz, 6 H), 1.11-1.18 (m, 1 H), 1.58-1.72 (m, 1 H), 4.20-4.26 (m, 2 H), 5.90 (s, 2 H), 7.16-7.21 (m, 1 H), 7.25-7.29 (m, 3 H), 7.34-7.39 (m, 1 H), 7.57 (dt, J = 1.0, 8.2, 1 H), 7.57 (d, J = 8.5, 1 H), 7.77-7.82 (m, 1 H);
25

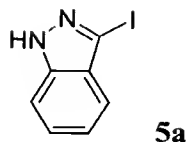
IR (KBr, cm⁻¹) 2951, 1615, 1472, 1460, 1325, 1247, 1168, 973, 766, 738;

MS m/e 399 (MH⁺);

Anal. Calcd for C₂₀H₂₁BrN₄ : C, 60.46; H, 5.33; N, 14.10

Found: C, 60.30; H, 5.46; N, 14.05.

34



3-iodoindazole (**5a**) was prepared using the same procedure as compound **4a** with iodine in 89% yield:

5

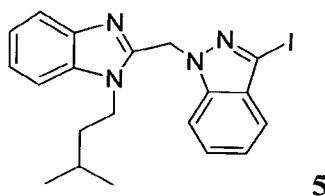
^1H NMR (CDCl_3) δ 7.21-7.27 (m, 1 H), 7.43-7.60 (m, 3 H);

IR (KBr, cm^{-1}) 3153, 2933, 2903, 1620, 1472, 1344, 1321, 1239, 1013, 899, 769, 747, 738;

MS m/e 243 (MH^+);

10

Anal. Calcd for $\text{C}_7\text{H}_5\text{IN}_2$:	C, 34.45; H, 2.07; N, 11.45
Found:	C, 34.62; H, 1.97; N, 11.38.



15

Compound **5** was prepared as an off-white solid using the same procedure as compound **4** with 3-iodoindazole (**5a**) in 54% yield:

^1H NMR (CDCl_3) δ 0.90 (d, J = 6.6 Hz, 6 H), 1.07-1.15 (m, 2 H), 1.60-1.66 (m, 1 H), 4.18-4.24 (m, 2 H), 5.94 (s, 2 H), 7.18 (t, J = 7.5 Hz, 1 H), 7.25-7.28 (m, 3 H), 7.37 (td, J = 7.7, 1.0 Hz, 1 H), 7.44 (d, J = 8.2 Hz, 1 H), 7.65 (d, J = 8.5 Hz, 1 H), 7.78-7.81 (m, 1 H);

20

IR (KBr, cm^{-1}) 2951, 1614, 1505, 1462, 1167, 967, 740;

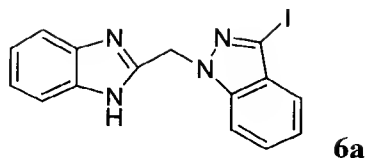
MS m/e 445 (MH^+);

Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{IN}_4$:

25

Found:	C, 54.06; H, 4.76; N, 12.61
	C, 53.90; H, 4.82; N, 12.35.

35



Compound **6a** was prepared using the same procedure as compound **1c** with 3-iodoindazole (**5a**) in 34% yield:

5

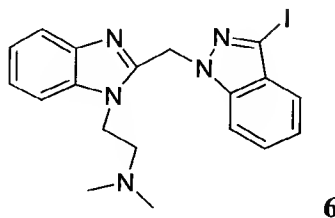
^1H NMR (DMSO- d_6) δ 5.92 (s, 2 H), 7.15-7.18 (m, 2 H), 7.27 (t, $J = 4.7$ Hz, 1 H), 7.46-7.53 (m, 4 H), 7.82 (d, $J = 5.2$ Hz, 1 H);

IR (KBr, cm^{-1}) 2830, 2625, 1613, 1538, 1490, 1457, 1445, 1276, 749;

MS m/e 375 (MH^+);

10 Anal. Calcd for $\text{C}_{15}\text{H}_{11}\text{I} \cdot 0.25\text{H}_2\text{O}$: C, 47.57; H, 3.06, N, 14.79

Found: C, 47.47; H, 2.93, N, 14.52.



15 Compound **6** was prepared as a yellow solid using the same procedure as compound **1** with compound **6a** and 2-chloro- N,N -dimethylethylamine hydrochloride in 51% yield:

20 ^1H NMR (CDCl_3) δ 2.27 (s, 6 H), 2.31 (t, $J = 7.2$ Hz, 2 H), 4.36 (t, $J = 7.0$ Hz, 2 H), 5.96 (s, 2 H), 7.18-7.46 (m, 6 H), 7.67 (bd, $J = 9.3$ Hz, 1 H), 7.77-7.80 (m, 1 H);

IR (KBr, cm^{-1}) 3435, 1613, 1460, 1423, 1248, 1165, 740;

MS m/e 446 (MH^+);

Anal. Calcd for $\text{C}_{19}\text{H}_{20}\text{IN}_5$: C, 51.25; H, 4.53; N, 15.73

25 Found: C, 51.25; H, 4.51; N, 15.38.

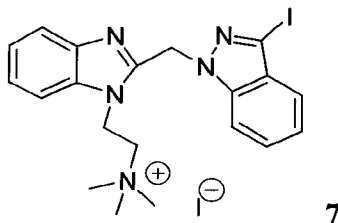
The amine **6** and excess 4N HCl in dioxane were stirred in MeOH. The solvent was evaporated and the residue dried under vacuum to give the HCl salt of compound **6**:

- 5 ^1H NMR (CD_3OD) δ 3.13 (s, 6 H), 3.76-3.82 (m, 2 H), 5.17-5.23 (m, 2 H), 6.41 (s, 2 H), 7.35-7.40 (m, 1 H), 7.56-7.76 (m, 5 H), 7.92 (d, $J = 8.5$ Hz, 1 H), 8.09 (d, $J = 7.9$ Hz, 1 H);

IR (KBr, cm^{-1}) 3400, 2675, 1613, 1489, 1460, 1316, 1172, 970, 755;

MS m/e 446 (MH^+);

- 10 Anal. Calcd for $\text{C}_{19}\text{H}_{20}\text{IN}_5 \cdot 2\text{HCl} \cdot 0.5\text{H}_2\text{O}$: C, 43.28; H, 4.40, N, 13.28
Found: C, 43.22; H, 4.53, N, 13.17.



- 15 A mixture of the compound **6** (50 mg, 0.11 mmol) and methyl iodide (16 mg, 0.11 mmol) in acetone (1 mL) was stirred at room temperature for 17 hours. Collection of the solid by filtration gave 50 mg (77% yield) of compound **7** as a pale yellow solid:

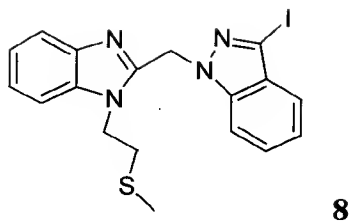
- 20 ^1H NMR (CD_3OD) δ 3.32 (s, 9 H), 3.70-3.75 (m, 2 H), 5.01-5.07 (m, 2 H), 6.07 (s, 2 H), 7.27-7.59 (m, 5 H), 7.64 (d, $J = 7.8$ Hz, 1 H), 7.70 (d, $J = 7.5$ Hz, 1 H), 7.85 (d, $J = 8.6$ Hz, 1 H);

IR (KBr, cm^{-1}) 3435, 3011, 1615, 1489, 1475, 1459, 1414, 1248, 1168, 965, 755;

MS m/e 459 (M^+);

- 25 Anal. Calcd for $\text{C}_{20}\text{H}_{23}\text{I}_2\text{N}_5$: C, 40.91; H, 3.95; N, 11.93
Found: C, 40.87; H, 3.96; N, 11.65.

37



Compound **8** was prepared using the same procedure as compound **1** with compound **6a** and 2-chloroethyl methyl sulfide in 70% yield:

5

^1H NMR (CDCl_3) δ 2.14 (s, 3 H), 2.63 (t, $J = 7.1$ Hz, 2 H), 4.61 (t, $J = 7.1$ Hz, 2 H), 6.14 (s, 2 H), 7.20 (t, $J = 7.1$ Hz, 1 H), 7.36-7.47 (m, 5 H), 7.84-7.89 (m, 2 H);

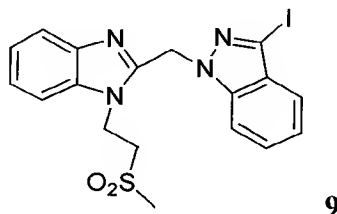
IR (KBr, cm^{-1}) 1613, 1460, 1426, 1331, 1163, 755, 743;

10

MS m/e 449 (MH^+);

Anal. Calcd for $\text{C}_{18}\text{H}_{17}\text{IN}_4\text{S} \cdot 0.25\text{H}_2\text{O}$: C, 47.74; H, 3.90; N, 12.37

Found: C, 47.64; H, 3.77; N, 12.23.



15

A mixture of compound **8** (75 mg, 0.17 mmol) and magnesium monoperoxyphthalate hexahydrate (MMPP, 165 mg, 0.33 mmol) in DMF (3 mL) was stirred at room temperature for 17 hours. The reaction mixture was diluted with EtOAc and washed with water. The organic layer was separated, dried over MgSO_4 , and evaporated. Column chromatography (EtOAc/hexanes, 2:1) gave compound **9**:

20

^1H NMR (CDCl_3) δ 2.97 (s, 3 H), 3.26 (bt, $J = 7.6$ Hz, 2 H), 4.88 (bt, $J = 7.6$ Hz, 2 H), 5.97 (s, 2 H), 6.92-7.51 (m, 6 H), 7.74-7.82 (m, 2 H);

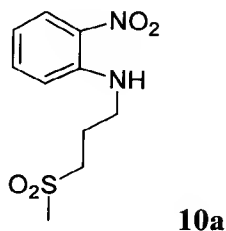
IR (KBr, cm^{-1}) 1458, 1318, 1294, 1167, 1133, 966, 766, 742;

MS m/e 481 (MH^+);

Anal. Calcd for $\text{C}_{18}\text{H}_{17}\text{IN}_4\text{O}_2\text{S}\cdot 0.25\text{H}_2\text{O}$: C, 45.01; H, 3.57; N, 11.66

Found: C, 44.83; H, 3.58; N, 11.38.

5



2-Fluoronitrobenzene (35.4 g, 250.9 mmol), 3-(methylthio)propylamine (24.0g, 228.1 mmol) and potassium carbonate (47.3 g, 342 mmol) were stirred in
10 CH_3CN (100 mL) at room temperature for 18 hours. After stirring for an additional hour at reflux, the mixture was cooled to room temperature and filtered. The filtrate was evaporated. To the residue in DMF (150 mL), monoperoxyphthalic acid magnesium hexahydrate (168 g, 340 mmol) was added in several portions with ice-water cooling. The mixture was stirred at room
15 temperature for 3 hours and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 and washed with 1 N NaOH, water, brine, dried over MgSO_4 , and evaporated. The residue was triturated in hot EtOAc to give **10a** (48.7 g, 75% yield) as an orange solid:

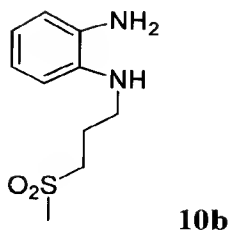
20 ^1H NMR (CDCl_3) δ 2.25-2.35 (m, 2 H), 2.97 (s, 3 H), 3.17 (t, $J = 7.2$ Hz, 2 H), 3.59 (t, $J = 6.9$ Hz, 2 H), 6.68-6.74 (m, 1 H), 6.89 (d, $J = 8.1$ Hz, 1 H), 7.45-7.51 (m, 1 H), 8.20 (dd, $J = 1.5, 8.7$ Hz, 1 H);

MS m/e 259 (MH^+);

Anal. Calcd for $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_4\text{S}$: C, 46.50; H, 5.46; N, 10.84

25 Found: C, 46.53; H, 5.54; N, 10.90.

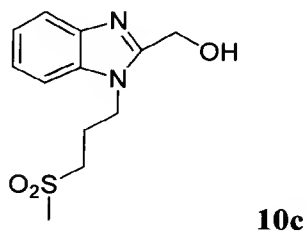
39



To a suspension of **10a** (48.5 g, 187.8 mmol) in a mixture of CHCl_3 and MeOH (150 mL, 1:3) was added 10% palladium on carbon (6 g) under nitrogen.

- 5 The reduction was carried out in a Parr shaker with hydrogen pressure maintained between 40 and 60 psi for 25 min. The catalyst was removed by filtration and the filtrate was evaporated to give crude **10b**:

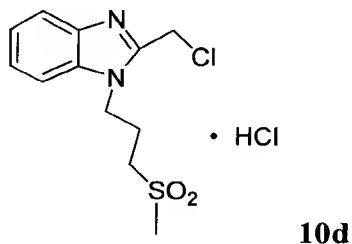
- ^1H NMR (CD_3OD) δ 2.11-2.21 (m, 2 H), 2.98 (s, 3 H), 3.28-3.36 (m, 4 H), 6.75
10 (dt, $J = 0.9, 7.2$ Hz, 1 H), 6.85 (d, $J = 7.5$ Hz, 1 H), 7.06-7.12 (m, 2 H);
MS m/e 229 (MH^+).



- 15 Diamine **10b** was stirred at reflux for 18 hours with glycolic acid (15.7 g, 207 mmol) in 6 N HCl (150 mL). The solution was cooled in an ice bath and
neutralized with concentrated NH_4OH solution, extracted with EtOAc, dried over
 MgSO_4 , and evaporated. The residue was purified by chromatography (gradient,
EtOAc: hexane = 1:1, EtOAc, then EtOAc:MeOH = 10:1) to give a product which
20 crystallized from EtOAc/MeOH to afford 25.7 g (51% yield over two steps) of
compound **10c**:

^1H NMR (CD_3OD) δ 2.38-2.44 (m, 2 H), 2.97 (s, 3 H), 3.24 (t, $J = 7.6$ Hz, 2 H), 4.54 (t, $J = 7.6$ Hz, 2 H), 7.27 (t, $J = 1.1, 8.1$ Hz, 1 H), 7.33 (dt, $J = 1.1, 8.0$ Hz, 1 H), 7.62 (d, $J = 8.1$ Hz, 1 H), 7.64 (dd, $J = 1.0, 8.0$ Hz, 1 H);
MS m/e 269 (MH^+).

5

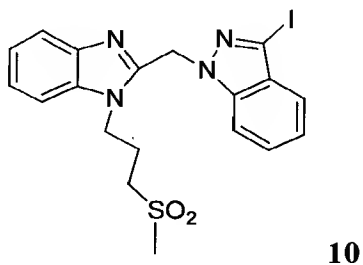


Compound **10d** was prepared using the same procedure as compound **4c** with alcohol **10c**:

10

^1H NMR (CD_3OD) δ 2.46-2.52 (m, 2 H), 3.03 (s, 3 H), 3.37 (t, $J = 7.1$ Hz, 2 H), 4.77 (t, $J = 7.8$ Hz, 2 H), 5.31 (s, 2 H), 7.68-7.73 (m, 2 H), 7.86 (dd, $J = 2.8, 6.9$ Hz, 1 H), 8.03 (dd, $J = 1.7, 6.1$ Hz, 1 H);
MS m/e 287 (MH^+).

15

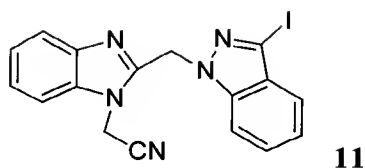


Compound **10** was prepared using the same procedure as compound **4** with compound **5a** and compound **10d**:

20

^1H NMR (CDCl_3) δ 1.88-2.00 (m, 2 H), 2.85 (s, 3 H), 3.05-3.10 (m, 2 H), 4.76-4.81 (m, 2 H), 6.35 (s, 2 H), 7.08-7.27 (m, 1 H), 7.25 (d, $J = 8.4$ Hz, 1 H), 7.37-7.44 (m, 3 H), 7.54-7.57 (m, 1 H), 7.77-7.80 (m, 1 H), 8.34 (d, $J = 8.7$ Hz, 1 H);

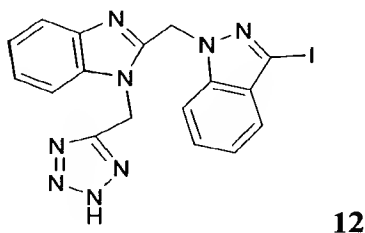
MS m/e 495 (MH^+).



Compound **11** was prepared using the same procedure as compound **1** with compound **6a** and bromoacetonitrile in 42% yield:

1H NMR ($CDCl_3$) δ 5.42 (s, 2 H), 5.93 (s, 2 H), 7.19-7.47 (6 H), 7.67 (d, J = 8.7 Hz, 1 H), 7.79 (dd, J = 2.1, 6.6 Hz, 1 H);

IR (KBr, cm^{-1}) 3435, 1615, 1464, 1412, 1198, 752, 741.



A mixture of compound **11** (310 mg, 0.75 mmol), sodium azide (146 mg, 2.25 mmol), and ammonium chloride (120 mg, 2.25 mmol) in DMF (15 mL) was stirred at 110 °C for 16 hours. The solid was filtered and the filtrate was evaporated under vacuum. The residue was dissolved in 1N NaOH and the aqueous solution was washed with EtOAc. The aqueous solution was adjusted to pH 7 and then extracted with EtOAc. The organic extracts were dried over $MgSO_4$ and evaporated to give 260 mg of crude product which was converted to sodium salt by adding 1N NaOH (0.54 mL, 0.54 mmol) in MeOH (5 mL). The solvent was evaporated and the residue was purified by C18 column chromatography to give 40 mg of compound **12** as the sodium salt:

1H NMR (CD_3OD) δ 5.84 (s, 2 H), 6.19 (s, 2 H), 7.20-7.30 (m, 3 H), 7.47-7.60 (m, 4 H), 7.70 (d, J = 8.9 Hz, 1 H);

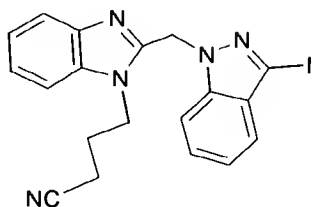
IR (KBr, cm^{-1}) 3368, 1615, 1462, 1321, 1247, 1168, 741;

MS m/e 457 (MH^+);

Anal. Calcd for $\text{C}_{17}\text{H}_{13}\text{IN}_8\text{Na} \cdot 1.75 \text{ H}_2\text{O}$: C, 40.06; H, 3.06; N, 21.98

Found: C, 40.30; H, 3.33; N, 21.66.

5



13

Compound **13** was prepared using the same procedure as compound **1** with compound **6a** and 4-bromobutyronitrile:

10

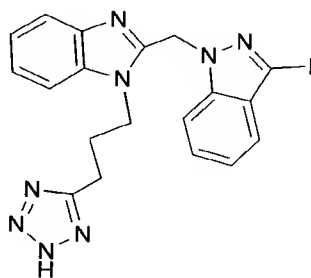
^1H NMR (CDCl_3) δ 1.59-1.69 (m, 2 H), 2.38 (t, $J = 7.0$ Hz, 2 H), 4.45 (t, $J = 8.7$ Hz, 2 H), 5.94 (s, 2 H), 7.20-7.48 (m, 6 H), 7.72 (d, $J = 8.5$ Hz, 1 H), 7.79-7.84 (m, 1 H);

IR (KBr, cm^{-1}) 3424, 2943, 1614, 1459, 1418, 1166, 742;

15 MS m/e 442 (MH^+);

Anal. Calcd for $\text{C}_{19}\text{H}_{16}\text{IN}_5$: C, 51.72; H, 3.65; N, 15.87

Found: C, 51.63; H, 3.87; N, 15.61.



14

20

Compound **14** was prepared using the same procedure as compound **12** with compound **13**:

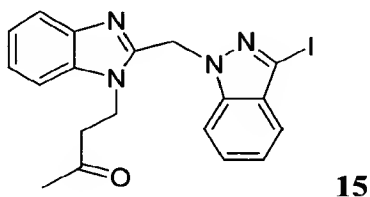
^1H NMR (CD_3OD) δ 1.94-2.03 (m, 2 H), 2.85 (t, $J = 7.2$ Hz, 2 H), 4.37 (t, $J = 7.7$ Hz, 2 H), 5.98 (s, 2 H), 7.23-7.32 (m, 3 H), 7.39-7.52 (m, 3 H), 7.60-7.69 (m, 2 H);

IR (KBr, cm^{-1}) 3395, 1615, 1459, 1327, 1167, 743;

5 MS m/e 485 (MH^+);

Anal. Calcd for $\text{C}_{19}\text{H}_{16}\text{IN}_8\text{Na}\cdot 3.00 \text{ H}_2\text{O}$: C, 41.05; H, 4.08; N, 19.54

Found: C, 41.03; H, 3.87; N, 19.24.



10

Compound **6a** (800 mg, 2.14 mmol) and methyl vinyl ketone (600 mg, 8.55 mmol) were refluxed in EtOH (25 mL) for 18 hours. The solvent was evaporated to give a tan solid. This solid was triturated with Et_2O and filtered to give 825 mg (87% yield) of compound **15**:

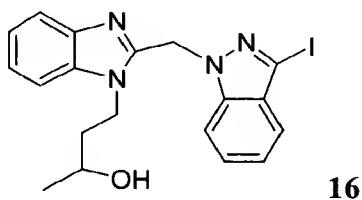
15

^1H NMR (CDCl_3) δ 2.09 (s, 3 H), 2.58 (t, $J = 7.1$ Hz, 2 H), 4.59 (t, $J = 7.1$ Hz, 2 H), 6.03 (s, 2 H), 7.20-7.30 (m, 4 H), 7.41-7.48 (m, 2 H), 7.77-7.81 (m, 2 H);
IR (KBr, cm^{-1}) 3396, 1702, 1614, 1420, 1461, 1368, 1323, 1247, 1166, 1151, 742;

20 MS m/e 445 (MH^+);

Anal. Calcd for $\text{C}_{19}\text{H}_{17}\text{IN}_4\text{O}$: C, 51.37; H, 3.86; N, 12.61

Found: C, 51.48; H, 3.91; N, 12.50.



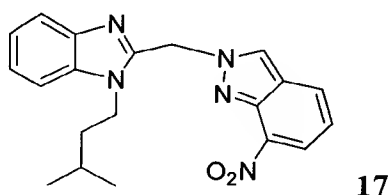
25

Ketone **15** (300 mg, 0.68 mmol) was suspended in MeOH (10 mL) and cooled to 0 °C with an ice bath. Sodium borohydride (25 mg, 0.68 mmol) was added and the reaction mixture was allowed to stir while warming to room temperature. The solvent was evaporated. The residue was diluted with water and extracted with Et₂O. The organic extracts were dried over MgSO₄ and evaporated. Trituration with Et₂O followed by filtration gave 210 mg (70% yield) of compound **16**:

¹H NMR (CDCl₃) δ 1.18 (d, J = 6.2 Hz, 3 H), 1.52-1.56 (m, 2 H), 3.78-3.82 (m, 1 H), 4.12-4.53 (m, 2 H), 5.99 (q, J = 15.2 Hz, 2 H), 7.21 (t, J = 7.6 Hz, 1 H), 7.27-7.30 (m, 1 H), 7.37-7.39 (m, 1 H), 7.42-7.46 (m, 2 H), 7.77-7.81 (m, 2 H); IR (KBr, cm⁻¹) 3392, 2960, 2925, 1614, 1461, 1421, 1323, 1248, 1165, 742; MS m/e 447 (MH⁺);

Anal. Calcd for C₁₉H₁₉IN₄O: C, 51.13; H, 4.29; N, 12.55

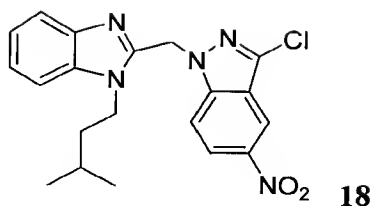
Found: C, 50.93; H, 4.22; N, 12.27.



Compound **17** was prepared using the same procedure as compound **4** with 7-nitroindazole in 20% yield:

¹H NMR (CDCl₃) δ 0.82 (d, J = 6.6 Hz, 6 H), 1.25-1.40 (m, 2 H), 1.53-1.68 (m, 1 H), 4.27-4.32 (m, 2 H), 6.00 (s, 2 H), 7.12 (t, J = 7.9 Hz, 1 H), 7.19-7.30 (m, 3 H), 7.69-7.73 (m, 1 H), 7.92 (dd, J = 0.8, 8.3 Hz, 1 H), 8.28 (dd, J = 0.9, 7.6 Hz, 1 H), 8.31 (s, 1 H); IR (KBr, cm⁻¹) 2957, 1728, 1516, 1455, 1407, 1335, 1301, 1138, 737; MS m/e 364 (MH⁺).

45



Compound **18** was prepared using the same procedure as compound **4** with 3-chloro-5-nitroindazole in 33% yield:

5

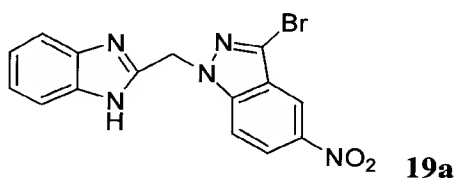
^1H NMR (CDCl_3) δ 0.90 (d, J = 6.6 Hz, 6 H), 1.18-1.28 (m, 2 H), 1.58-1.71 (m, 1 H), 4.19-4.25 (m, 2 H), 5.82 (s, 2H), 7.19-7.25 (m, 3 H), 7.69-7.72 (m, 1 H), 7.79 (d, J = 9.3 Hz, 1 H), 8.19 (dd, J = 2.1, 9.3 Hz, 1 H), 8.57 (d, J = 2.1, 1 H);

IR (KBr, cm^{-1}) 2956, 1586, 1616, 1524, 1459, 1339, 794, 749;

10 MS m/e 398 (MH^+);

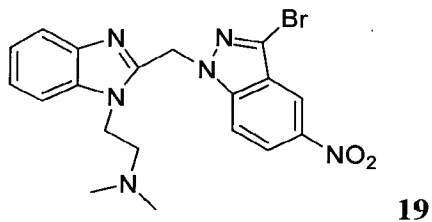
Anal. Calcd for $\text{C}_{20}\text{H}_{20}\text{N}_5\text{O}_2\text{Cl}$: C, 60.38; H, 5.07; N, 17.60

Found: C, 60.67; H, 5.42; N, 17.03.



15

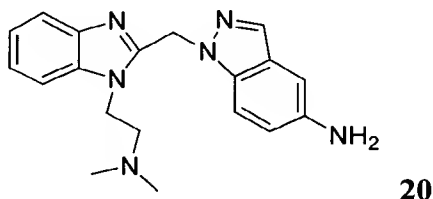
Compound **19a** was prepared using the same procedures as compound **1c** with 3-bromo-5-nitroindazole and was used without further purification.



20

Compound **19** was prepared using the same procedures as compound **1** with compound **19a** and 2-chloro-N,N-dimethylethylamine hydrochloride in 25% yield:

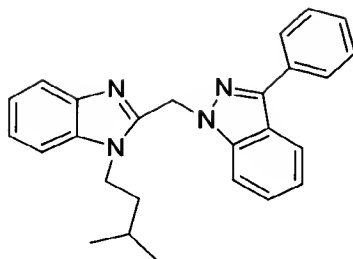
- 5 ^1H NMR (CDCl_3) δ 2.32 (s, 6 H), 2.49 (bt, 2 H), 4.42 (bt, 2 H), 5.97 (s, 2 H), 7.28-7.33 (m, 3 H), 7.75-7.79 (m, 1 H), 7.88 (d, $J = 9.3$ Hz, 1 H), 8.27 (dd, $J = 2.1, 9.3$ Hz, 1 H), 8.57 (d, $J = 2.1$ Hz, 1 H);
IR (KBr, cm^{-1}) 2943, 2772, 1616, 1517, 1456, 1340, 1277, 737;
MS m/e 443 (MH^+);
- 10 Anal. Calcd for $\text{C}_{19}\text{H}_{21}\text{BrN}_6\text{O}_2$: C, 51.25; H, 4.75, N, 18.87
Found: C, 51.38; H, 4.45, N, 18.88.



- 15 Compound **19** (40 mg, 0.09 mmol) was reduced in a Parr apparatus under H_2 in the presence of 10% palladium on carbon (40 mg) in a mixture of MeOH and CHCl_3 (2.4 mL, 5:1) for 2 hours at 35 psi. The catalyst was removed by filtration through a pad of celite and the filtrate was evaporated to give compound **20**:

- 20 ^1H NMR (CDCl_3) δ 3.12 (s, 6 H), 3.57-3.65 (m, 2 H), 5.00-5.06 (m, 2 H), 6.19 (s, 2 H), 7.35-7.49 (m, 2 H), 7.67 (d, $J = 7.8$ Hz, 1 H), 7.79 (d, $J = 8.0$ Hz, 1 H), 7.87 (s, 1 H), 8.06 (d, $J = 8.9$ Hz, 1 H), 8.29 (s, 1 H);
MS m/e 335 (MH^+).

47

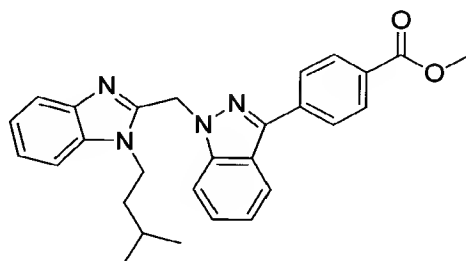
**21**

A mixture of compound **4** (40 mg, 0.10 mmol), phenyltrimethyltin (29 mg, 0.12 mmol), and palladium tetrakis(triphenylphosphine) (12 mg, 0.01 mmol) in toluene (2 ml) was heated to reflux for 3 hours. The reaction mixture was diluted with EtOAc (10 ml), washed with saturated NaHCO₃, dried over MgSO₄, and concentrated. The residue was purified by prep-HPLC (gradient, 10% MeOH in H₂O with 0.1% TFA to 90% MeOH in H₂O with 0.1% TFA) to give 34 mg (86% yield) of compound **21** as a pale yellow solid:

¹H NMR (CD₃OD) δ 0.77 (d, J = 6.6 Hz, 6 H), 1.30-1.40 (m, 2 H), 1.40-1.56 (m, 1 H), 4.45-4.50 (m, 2 H), 6.26 (s, 2 H), 7.32-7.58 (m, 8 H), 7.75 (m, 3 H), 7.91 (d, J = 6.9 Hz, 1 H), 8.07 (d, J = 8.1 Hz, 1 H);

IR (KBr, cm⁻¹) 2960, 1683, 1492, 1188, 1136, 749;

MS m/e 395 (MH⁺).

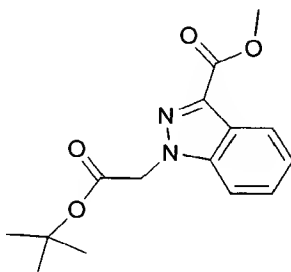
**22**

Compound **22** was prepared using the same procedure as compound **21** with 4-trimethylstannyl-benzoic acid methyl ester prepared according to the procedure described by Wursthorn, K.R. and Kuivila, H.G. (*J. Organomet. Chem.*, **1977**, 140 (1), 29-39):

^1H NMR (CDCl_3) δ 0.82 (d, $J = 6.6$ Hz, 6H), 1.18-1.25 (m, 2 H), 1.71-1.79 (m, 1 H), 3.97 (s, 3 H), 4.21-4.38 (m, 2 H), 6.00 (s, 2 H), 7.25-7.42 (m, 6 H), 7.71-7.84 (m, 2 H), 8.02-8.21 (m, 4 H);

MS m/e 453 (MH^+).

5

**23a**

A solution of indazole-3-carboxylic acid (Fluka, 3.0 g, 18.5 mmol) in MeOH (50 ml) with concentrated sulfuric acid (0.1 ml) was heated to reflux for 12 hours, cooled and concentrated. The residue was dissolved in EtOAc and washed with saturated NaHCO_3 , dried over MgSO_4 and concentrated to give 2.32 g (70% yield) of the methyl ester as a dark solid. The ester was dissolved in CH_3CN (50 mL), treated with K_2CO_3 (0.83 g, 6.0 mmol) and t-butyl bromoacetate (0.84 mL, 5.7 mmol), and stirred at room temperature for 12 hours. The solution was filtered and concentrated. The residue was purified by flash chromatography (gradient, hexanes:EtOAc = 20:1 to 5:1) to give 1.44 g (87% yield) of compound **23a**:

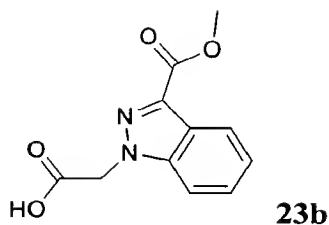
^1H NMR ($\text{DMSO}-d_6$) δ 1.41 (s, 9 H), 3.93 (s, 3 H), 5.44 (s, 2 H), 7.36 (t, $J = 7.1$ Hz, 1 H), 7.51 ($J = 7.2$ Hz, 1 H), 7.78 (d, $J = 8.1$ Hz, 1 H), 8.08 (d, $J = 8.1$ Hz, 1 H);

IR (KBr, cm^{-1}) 2986, 1746, 1720, 1230;

MS m/e 290 (MH^+);

Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_4$: C, 62.06; H, 6.25; N, 9.65

Found: C, 62.23; H, 6.27; N, 9.63.

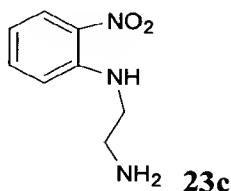


Compound **23a** (1.2 g, 4.13 mmol) was dissolved in TFA (5 mL) and stirred for 12 hours. The solution was concentrated to give 0.96 g (99% yield) of compound **23b**:

^1H NMR (DMSO- d_6) δ 3.93 (s, 3 H), 5.44 (s, 2 H), 7.36 (t, J = 7.1 Hz, 1 H), 7.50 (t, J = 7.1 Hz, 1 H), 7.80 (d, J = 8.2 Hz, 1 H), 8.09 (d, J = 8.2 Hz, 1 H);

IR (KBr, cm^{-1}) 1716, 1323, 1149, 747;

MS m/e 234 (MH^+).



A solution of 2-fluoronitrobenzene (30 mL, 2.84 mmol) in CH_3CN (30 mL) was added to a solution of ethylenediamine (76 mL, 1.14 mmol) in CH_3CN (50 mL). The mixture was stirred at room temperature for 12 hours then concentrated to give 51 g (99% yield) of the product **23c** as an orange oil:

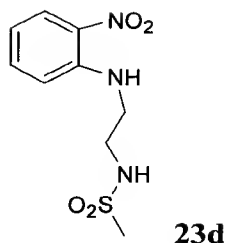
^1H NMR (DMSO- d_6) δ 2.82 (t, J = 6.0 Hz, 2 H), 3.30 (t, J = 6.0 Hz, 2 H), 6.66 (t, J = 8.4 Hz, 1 H), 7.05 (d, J = 8.7 Hz, 1 H), 7.53 (d, J = 8.4 Hz, 1 H), 8.30-8.34 (m, 1 H);

IR (film, cm^{-1}) 1621, 1514, 1347, 740;

MS m/e 182 (MH^+);

Anal. Calcd for $\text{C}_8\text{H}_{11}\text{N}_3\text{O}_2 \cdot 0.20 \text{ H}_2\text{O}$: C, 51.99; H, 6.22; N, 22.74

Found: C, 51.99; H, 6.29; N, 22.46.



To a mixture of amine **23c** (2.0 g, 11 mmol) in CH₂Cl₂ (50 mL) was added triethyl amine (1.53 mL, 11 mmol) and the mixture was cooled to 0°C. Methanesulfonyl chloride (0.85 mL, 11 mmol) was added slowly. Once the addition was complete the reaction mixture was warmed to room temperature and stirred for 12 hours. The mixture was poured into water and the aqueous layer separated, dried over MgSO₄, and evaporated. The residue was chromatographed (3% MeOH in CH₂Cl₂) to give 2.55 g (89% yield) of **23d** as an orange oil:

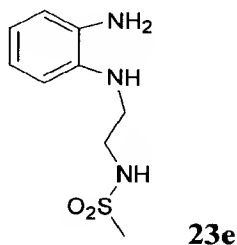
¹H NMR (DMSO-d₆) δ 2.91 (s, 3 H), 3.18 (dd, J = 6.1, 11.6 Hz, 2 H), 3.39-3.42 (m, 2 H), 6.70 (t, J = 9.0 Hz, 1 H), 7.08 (d, J = 8.5 Hz, 1 H), 7.28 (t, J = 6.1 Hz, exchanges with D₂O, 1 H), 7.55 (td, J = 1.0, 6.0, Hz, 1 H); 8.07 (dd, J = 1.0, 8.7 Hz, 1 H); 8.23 (bs, 1H exchanges with D₂O);

IR (film, cm⁻¹) 1511, 1354, 1317, 1151;

MS m/e 260 (MH⁺);

Anal. Calcd for C₉H₁₃N₃O₄S•0.5 H₂O•0.08 EtOAc: C, 40.66; H, 5.36; N, 15.26

Found: C, 40.58; H, 5.29; N, 14.88.



A mixture of compound **23d** (1.0 g, 3.9 mmol) and 10% palladium on carbon (100 mg) in EtOH (50 mL) was hydrogenated at 50 psi for 12 hours. The

mixture was filtered and the filtrate was evaporated to give an orange oil. The residue was chromatographed (1% MeOH in CH₂Cl₂) to give 0.55g (62% yield) of compound **23e** as a dark oil:

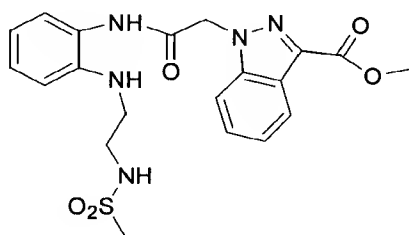
- 5 ¹H NMR (DMSO-d₆) δ 2.91 (s, 3 H), 3.17 (bs, 2 H), 4.45 (bs, 3 H, 1H exchanges with D₂O), 6.40-6.56 (m, 4 H), 7.11 (bs, 1 H, exchanges with D₂O);

IR (film, cm⁻¹) 3326, 1625, 1510, 1315, 1148, 738;

MS m/e 230 (MH⁺);

Anal. Calcd for C₉H₁₅N₃O₂S: C, 46.78; H, 6.63; N, 18.18

10 Found: C, 46.81; H, 6.79; N, 17.81.



23f

- Compound **23b** (0.4 g, 1.7 mmol) and thionyl chloride (5 mL) were stirred at reflux for 30 minutes. The excess thionyl chloride was evaporated *in vacuo* to give the corresponding acid chloride. Diamine **23e** was dissolved in CH₂Cl₂ (10 mL), treated with Et₃N (0.21 g, 2.0 mmol) and cooled to -78°C. A solution of the acid chloride in CH₂Cl₂ (10 mL) was added dropwise. The reaction mixture was stirred at -78°C for 1 hour, then warmed to room temperature and stirred for 12 hours. The precipitate was filtered to give 0.33 g (44% yield) of compound **23f**:

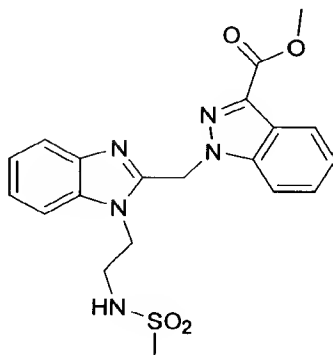
- ¹H NMR (DMSO-d₆) δ 2.91 (s, 3 H), 3.13-3.17 (m, 2 H), 3.21-3.32 (m, 2 H), 3.93 (s, 3 H), 5.26 (t, J = 5.6 Hz, 1 H, exchanges with D₂O), 5.49 (s, 2 H), 6.57 (t, J = 7.6 Hz, 1 H), 6.68 (d, J = 8.0, 1 H), 7.02-7.18 (m, 4 H, 1 H exchanges with D₂O), 7.36 (t, J = 7.7 Hz, 1 H), 7.52 (t, J = 7.8 Hz, 1 H), 7.80 (d, J = 8.5 Hz, 1 H), 8.09 (d, J = 8.2 Hz, 1 H), 9.57 (s, 1 H, exchanges with D₂O);

IR (KBr, cm⁻¹) 1730, 1681, 1541, 1311, 1169;

MS m/e 445 (MH⁺);

Anal. Calcd for $C_{20}H_{23}N_5O_5S$: C, 53.92; H, 5.20; N, 15.72

Found: C, 53.57 ; H, 5.22; N, 15.58.

**23**

5

Compound **23f** was dissolved in AcOH (20 mL) and heated to reflux for 4 hours. The mixture was cooled and concentrated. The residue was purified by flash chromatography (gradient, MeOH/ CH_2Cl_2 , 3% to 5%) to give 240 mg (85% yield) of compound **23** as a white foam:

10

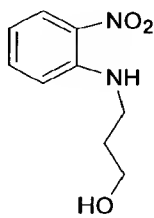
1H NMR (DMSO- d_6) δ 2.83 (s, 3 H), 3.34-3.39 (m, 2 H), 4.48-4.52 (m, 2 H), 6.21 (s, 2 H), 7.16 (t, J = 7.9 Hz, 1 H), 7.26 (t, J = 7.2 Hz, 1 H), 7.35-7.45 (m, 2 H), 7.48-7.53 (m, 2 H), 7.61 (d, J = 8.0 Hz, 1 H), 8.11 (d, J = 8.2 Hz, 1 H), 11.97 (s, 1 H, exchanges with D_2O);

15 IR (KBr, cm^{-1}) 1716, 1323, 1149, 747;

MS m/e 427 (MH^+);

Anal. Calcd for $C_{20}H_{21}N_5O_4 \cdot 0.35 H_2O \cdot 0.53 AcOH$: C, 54.33; H, 5.16; N, 15.04

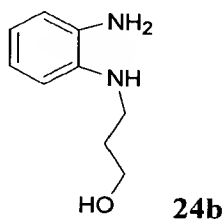
Found: C, 54.33; H, 5.16; N, 15.16.

**24a**

20

A solution of 2-fluoronitrobenzene (5.0 g, 35.5 mmol) and 1-amino-3-propanol (2.65 g, 35.5 mmol) in CH₃CN (100 mL) and triethylamine (4.1 g, 40 mmol) was heated to reflux for 12 hours, then cooled and concentrated. The residue was dissolved in EtOAc and washed with 1N HCl. The organic layer was dried over MgSO₄ and concentrated to give 6.5 g (93% yield) of compound **24a** as a dark orange solid:

¹H NMR (DMSO-d₆) δ 1.95-2.10 (m, 2 H), 3.48 (t, J = 6.7 Hz, 2 H), 3.86 (t, J = 6.7 Hz, 2 H), 6.61-6.67 (m, 1 H), 6.90 (d, J = 9 Hz, 1 H), 7.41-7.47 (m, 1 H), 8.17 (d, J = 7.8 Hz, 1 H);
IR (KBr cm⁻¹) 3378, 1512, 1353, 1069;
MS m/e 196 (MH⁺).



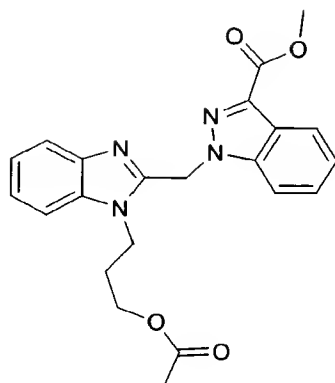
15

A solution of compound **24a** (6.5 g, 33.1 mmol) in EtOH (50 mL) was hydrogenated at 40 psi with 10% palladium on carbon (100 mg) for 4 hours. The catalyst was removed by filtration and the filtrate was evaporated to give 2.7 g (38% yield) of compound **24b** as a dark oil:

20

¹H NMR(DMSO-d₆) δ 1.90-1.94 (m, 2 H), 3.27 (t, J = 6.4 Hz, 2 H), 3.83 (t, J = 5.9 Hz, 2 H), 6.67-6.73 (m, 3 H) 6.81-6.85 (m, 1 H);
MS m/e 166 (MH⁺).

54

**24**

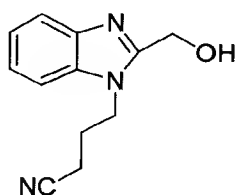
Compound **24** was prepared using the same sequence as compound **23** with compound **23b** and compound **24b**:

5

^1H NMR (DMSO- d_6) δ 1.86-1.98 (m, 2 H), 1.99 (s, 3 H), 3.91 (s, 3 H), 3.98 (t, J = 6.2 Hz, 2 H), 4.42 (t, J = 7.4 Hz, 2 H), 6.18 (s, 2 H), 7.15-7.28 (m, 2 H), 7.38 (t, J = 7.5 Hz, 1 H), 7.50-7.58 (m, 2 H), 7.90 (d, J = 8.5 Hz, 1 H), 8.10 (d, J = 8.1 Hz, 1 H);

10 IR (KBr, cm^{-1}) 1740, 1723, 740;MS m/e 406 (MH^+);Anal. Calcd for $\text{C}_{22}\text{H}_{22}\text{N}_4\text{O}_4$: C, 65.01; H, 5.46; N, 13.78

Found: C, 64.87; H, 5.56; N, 13.66.

**25a**

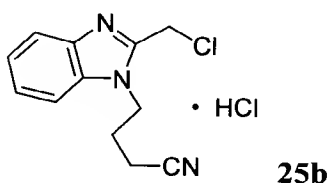
15

To a solution of 2-hydroxymethylbenzimidazole (29.63 g, 200 mmol) in a mixture of DMF/THF (150 mL, 1:1) was added sodium hydride (60% in mineral oil, 8.4 g, 210 mmol) in several portions at room temperature. After stirring for 1
20 hour, 4-bromobutyronitrile (29.6 g, 200 mmol) was added and the resulting solution was stirred at 80 $^{\circ}\text{C}$ for 18 hours. The solvent was evaporated. The

residue was diluted with H₂O and extracted with EtOAc. The combined extracts were dried over MgSO₄ and evaporated. The residue was purified by flash chromatography (EtOAc: hexane = 1:1 to 2:1, then EtOAc: MeOH = 10:1) to give 22.11 g (51% yield) of **25a** as a white solid:

5

¹H NMR (CDCl₃) δ 2.27-2.32 (m, 2 H), 2.41 (t, J = 6.0 Hz, 2 H), 4.41 (t, J = 7.2 Hz, 2 H), 7.26-7.38 (m, 3 H), 7.67-7.70 (m, 1 H);
MS m/e 216 (MH⁺).



10

To alcohol **25a** (22 g, 102.2 mmol) suspended in CH₂Cl₂ (100 mL) was slowly added thionyl chloride (15.81 g, 132.9 mmol) while cooling at 0 °C with an ice bath. The ice bath was removed and the solution was stirred at room temperature for 1 hour. The solvent was evaporated. The residue was triturated with EtOAc to give a nearly quantitative yield of **25b** as light gray powder:

15

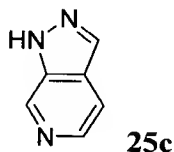
¹H NMR (CDCl₃) δ 2.32-2.38 (m, 2 H), 2.70 (t, J = 7.3 Hz, 2 H), 4.69 (t, J = 7.6 Hz, 2 H), 5.33 (s, 2 H), 7.69-7.74 (m, 2 H), 7.85-7.87 (m, 1 H), 8.00-8.02 (m, 1 H);

20

MS m/e 234 (MH⁺);

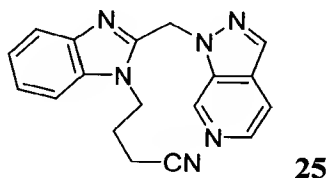
Anal. Calcd for C₁₂H₁₂N₃•HCl•0.25 H₂O: C, 52.48; H, 4.95; N, 15.30

Found: C, 52.52; H, 4.88; N, 15.26.



25

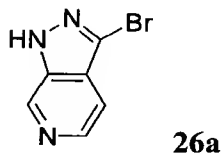
1H-pyrazolo[3,4-c]pyridine **25c** was prepared according to the procedure described by D. Chapman et al. (*Journal of the Chemical Society, Perkin Transactions I*, **1980**, 2398).



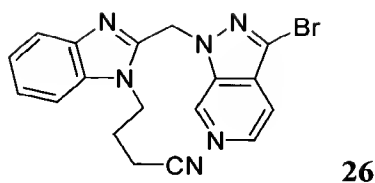
A suspension of 1H-pyrazolo[3,4-c]pyridine (**25c**, 24 mg, 0.20 mmol) and Cs₂CO₃ (196 mg, 0.60 mmol) in DMF (4 ml) was pre-mixed for 2 hours before compound **25b** (54 mg, 0.20 mmol) was added to the mixture. The reaction mixture was stirred at room temperature for 18 hours. The mixture was diluted with EtOAc (10 ml), washed with H₂O and brine, dried over MgSO₄, and concentrated. The crude product was purified by preparative HPLC (gradient, 10% MeOH in H₂O with 0.1% TFA to 90% MeOH in H₂O with 0.1% TFA) to yield 35 mg (55% yield) of compound **25** as a viscous oil:

¹H NMR (CD₃OD) δ 2.20-2.26 (m, 2H), 2.64 (t, J=7.2 Hz, 2H), 4.68 (t, J=7.6 Hz, 2H), 6.44 (s, 2H), 7.39-7.42 (m, 1H), 7.46-7.49 (m, 1H), 7.65 (d, J=8.1 Hz, 1H), 7.75 (d, J=8.2 Hz, 1H), 8.38 (d, J=6.2 Hz, 1H), 8.47 (d, J=6.2 Hz, 1H), 8.64 (s, 1H), 9.77 (s, 1H);

MS m/e 317 (MH⁺).



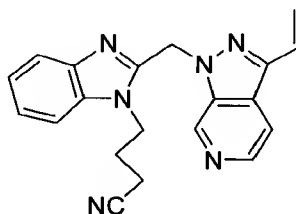
3-Bromo-1H-pyrazolo[3,4-c]pyridine **26a** was prepared the procedure described by D. Chapman et al. (*Journal of the Chemical Society, Perkin Transactions I*, **1980**, 2398).



Compound **26** was prepared using the same procedure as compound **25**
 5 with compound **25b** and compound **26a**:

^1H NMR (CDCl_3) δ 1.83-1.89 (m, 2H), 2.42 (t, $J=7.0$ Hz, 2H), 4.47 (t, $J=7.6$ Hz, 2H), 5.97 (s, 2H), 7.28-7.37 (m, 3H), 7.48-7.49 (m, 1H), 7.78-7.79 (m, 1H), 8.39 (d, $J=5.6$ Hz, 1H), 9.29 (d, $J=0.4$ Hz, 1H);

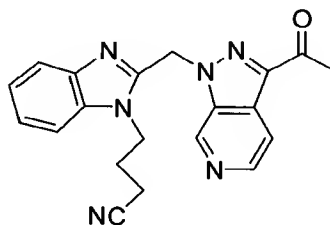
10 MS m/e 394, 396 (MH^+).



Compound **27** was prepared using the same procedure as Compound **21** starting
 15 with compound **26** and tributylvinyltin.

^1H NMR (CDCl_3) δ 1.73-1.79 (m, 2H), 2.33 (t, $J=7.0$ Hz, 2H), 4.45 (t, $J=7.6$ Hz, 2H), 5.63 (d, $J=11.4$ Hz, 1H), 5.99 (s, 2H), 6.14 (d, $J=18$ Hz, 1H), 6.99-7.04 (m, 1H), 7.29-7.34 (m, 3H), 7.75 (d, $J=5.6$ Hz, 1H), 7.80-7.82 (m, 1H), 8.37 (d, $J=5.6$ Hz, 1H), 9.27 (s, 1H);

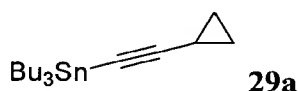
20 MS m/e 343 (MH^+).



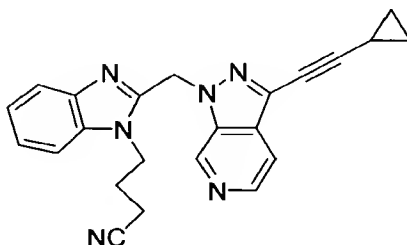
Compound **28** was prepared using the same procedure as compound **21** starting with compound **26** and tributyl(1-ethoxyvinyl)tin. The crude product formed was stirred in 25% HCl-MeOH for 2 h and purified by preparative-HPLC (gradient, 10% MeOH in H₂O with 0.1% TFA to 90% MeOH in H₂O with 0.1% TFA) to give the desired product (78%).

¹H NMR (CD₃OD) δ 2.31-2.38 (m, 2H), 2.69-2.73 (m, 5H), 4.76 (t, J=7.5 Hz, 2H), 6.59 (s, 2H), 7.44-7.48 (m, 1H), 7.52-7.55 (m, 1H), 7.66-7.69 (m, 1H), 7.83-7.85 (m, 1H), 8.61-8.65 (m, 2H), 9.80 (s, 1H);

MS m/e 359 (MH⁺).



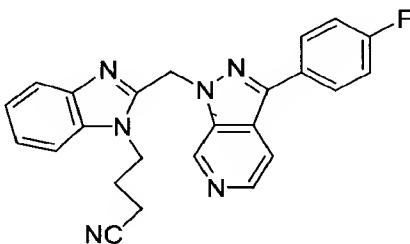
To a solution of 5-chloropentyne (2.05 g, 20.0 mmol) in THF (20 ml) at –28⁰C was added butyllithium (2.5 M in hexane, 16.4 ml, 41.0 mmol) dropwise. The formed solution was kept at 0⁰C for 1h before addition of tributyltin chloride (6.44 g, 19.8 mmol). The final solution was heated to reflux for 2 h, cooled down to the ambient temperature, diluted with EtOAc (200 ml). The organic layer was washed with aqueous NaHCO₃ saturated aqueous NaCl respectively, dried over MgSO₄, concentrated and was used as crude without further purification.



Compound **29** was prepared using the same procedure as compound **21** starting with compound **26** and tributyl-cyclopropylethyne-stannane.

^1H NMR (CD_3OD) δ 0.88-0.90 (m, 2H), 0.98-1.02 (m, 2H), 1.60-1.65 (m, 1H), 2.19-2.25 (m, 2H), 2.66 (t, $J=7.2$ Hz, 2H), 4.68 (t, $J=7.5$ Hz, 2H), 6.38 (s, 2H), 7.42-7.45 (m, 1H), 7.48-7.51 (m, 1H), 7.66 (d, $J=8.1$ Hz, 1H), 7.78 (d, $J=8.2$ Hz, 1H), 8.18-8.19 (m, 1H), 8.47 (d, $J=6.0$ Hz, 1H), 9.66 (s, 1H);

5 MS m/e 382 (MH^+).

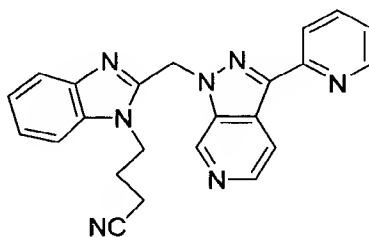
**30**

A mixture of compound **26** (40 mg, 0.1 mmol), 4-fluorophenylboronic acid (15 mg, 0.11 mmol), Cs_2CO_3 (49 mg, 0.15 mmol) and $\text{PdCl}_2(\text{PPh}_3)_2$ (7 mg, 0.01 mmol) in DMF (1 ml) was heated to 100°C for 4 h. Diluted with EtOAc (20 ml), washed with NaHCO_3 , H_2O , and brine. Dried over MgSO_4 and concentrated. The residue was purified by prep-HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) to give compound **30** 16 mg (39%).

15 ^1H NMR (CD_3OD) δ 2.24-2.30 (m, 2H), 2.64 (t, $J=7.1$ Hz, 2H), 4.72 (t, $J=7.6$ Hz, 2H), 6.45 (s, 2H), 7.30-7.34 (m, 2H), 7.39-7.42 (m, 1H), 7.46-7.49 (m, 1H), 7.64 (d, $J=8.1$ Hz, 1H), 7.76 (d, $J=8.2$ Hz, 1H), 8.07-8.10 (m, 1H), 8.51 (d, $J=6.2$ Hz, 1H), 8.55 (d, $J=6.2$ Hz, 1H), 9.72 (s, 1H);

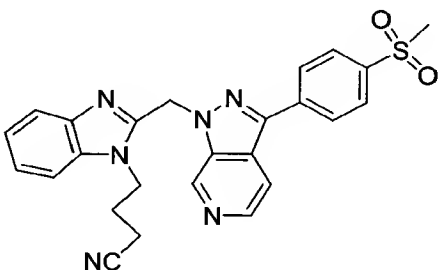
MS m/e 411 (MH^+).

20

**31**

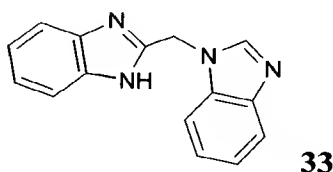
Compound **31** was prepared using the same procedure as compound **21** starting with compound **26** and tributyl(2-pyridio)tin.

^1H NMR (CD_3OD) δ 2.30-2.36 (m, 2H), 2.71 (t, $J=7.1$ Hz, 2H), 4.77 (t, $J=7.6$ Hz, 2H), 6.57 (s, 2H), 7.44-7.49 (m, 2H), 7.50-7.54 (m, 1H), 7.67 (d, $J=8.1$ Hz, 1H), 7.83 (d, $J=8.2$ Hz, 1H), 7.94-7.98 (m, 1H), 8.28 (d, $J=8.0$ Hz, 1H), 8.57-8.59 (m, 1H), 8.79 (d, $J=4.3$ Hz, 1H), 9.17-9.18 (m, 1H), 9.83 (s, 1H);
 MS m/e 394 (MH^+).



Compound **32** was prepared using the same procedure as compound **21** starting with compound **26** and 4-methylsulfonylphenylboronic acid.

^1H NMR (CD_3OD) δ 2.27-2.33 (m, 2H), 2.67 (t, $J=7.1$ Hz, 2H), 4.75 (t, $J=7.6$ Hz, 2H), 6.53 (s, 2H), 7.42-7.45 (m, 1H), 7.49-7.52 (m, 1H), 7.66 (d, $J=8.1$ Hz, 1H), 7.79 (d, $J=8.2$ Hz, 1H), 8.10-8.13 (m, 2H), 8.29-8.32 (m, 2H), 8.57-8.60 (m, 2H), 9.77 (s, 1H);
 MS m/e 471 (MH^+).



Compound **33** was prepared using the same procedure as compound **1c** starting with compound **1b** and benzimidazole:

^1H NMR (CDCl_3) δ 5.65 (s, 2H), 6.90-7.18 (m, 6H), 7.44 (s, 1H), 7.65 (bs, 2H);
 IR (KBr, cm^{-1}) 1493, 1459, 1437, 1330, 1273, 745;

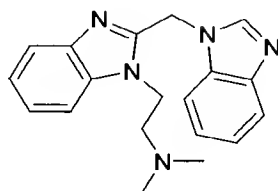
MS m/e 249 (MH^+);

Anal. Calcd for $C_{15}H_{12}N_4 \cdot 0.3 H_2O$:

C, 71.02; H, 5.01; N, 22.08

Found:

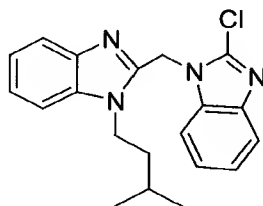
C, 70.96; H, 4.86; N, 21.93.



34

Compound **34** was prepared using the same procedure as compound **1** with compound **33** and 2-chloro-N,N-dimethylethylamine hydrochloride:

- 1H NMR (CD_3OD) δ 3.14 (s, 6H), 3.94 (t, $J = 7.6$ Hz, 2H), 5.14 (t, $J = 7.6$ Hz, 2H), 6.79 (s, 2H), 7.52-7.80 (m, 6H), 7.80-8.12 (m, 2H);
IR (KBr, cm^{-1}) 3400, 2680, 1617, 1551, 1464, 1368, 756;
MS m/e 320 (MH^+).



35

To a solution of 2-chlorobenzimidazole (71 mg, 0.46 mmol) and NaH (60% suspension in mineral oil, 19 mg, 0.46 mmol) in DMF (2 mL) was added compound **4c** and the reaction was stirred at room temperature for 5 days. The solvent was evaporated *in vacuo* and the residue was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, and concentrated. Purification by flash column chromatography (hexanes/EtOAc, 3:1) gave 43 mg (29% yield) of compound **35** as a white solid:

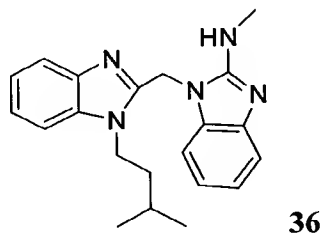
^1H NMR (CDCl_3) δ 0.83 (d, $J = 6.7$ Hz, 6 H), 1.06-1.14 (m, 2 H), 1.47-1.56 (m, 1 H), 4.05-4.11 (m, 2 H), 5.99 (s, 2 H), 7.21-7.30 (m, 2 H), 7.34-7.45 (m, 3 H), 7.54 (d, $J = 7.1$ Hz, 1 H), 7.69-7.72 (m, 1 H), 7.89-7.92 (m, 1 H);

IR (KBr, cm^{-1}) 3435, 2954, 1470, 1458, 1381, 744;

5 MS m/e 353 (MH^+);

Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{ClN}_4$: C, 68.08; H, 6.00; N, 15.88

Found: C, 67.82; H, 5.84; N, 15.58.



10

Compound **35** (150 mg, 0.43 mmol) and methylamine (165 mg, 2.13 mmol) were mixed in EtOH (2 mL) in a sealed tube. The reaction mixture was stirred at 125 °C for 18 hours. The EtOH was evaporated to give a light brown solid which was triturated with water to give 197 mg (100% yield) of compound

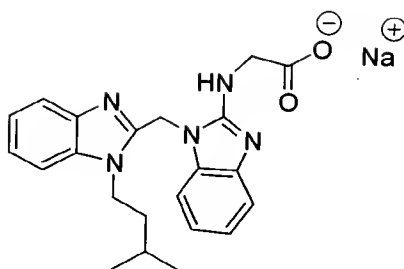
15 **36**:

^1H NMR ($\text{DMSO}-d_6$) δ 0.90 (d, $J = 6.6$ Hz, 6 H), 1.32-1.40 (m, 2 H), 1.57-1.64 (m, 1 H), 2.94 (d, $J = 4.4$ Hz, 3 H), 4.21-4.27 (m, 2 H), 5.57 (s, 2 H), 6.84 (t, $J = 7.2$ Hz, 1 H), 6.96 (t, $J = 7.2$ Hz, 1 H), 7.10-7.26 (m, 4 H), 7.50 (d, $J = 7.7$ Hz, 1 H), 7.56 (d, $J = 7.6$ Hz, 1 H);

20

IR (KBr, cm^{-1}) 3375, 2955, 1668, 1622, 1577, 1462, 1331, 739;

MS m/e 348 (MH^+).

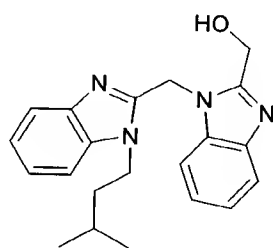


37

A mixture of glycine sodium salt hydrate (285 mg, 2.94 mmol) and compound **35** (207 mg, 0.59 mmol) in a mixture of water and EtOH (3 mL, 2:1) were stirred in a sealed tube at 120 °C for 9 days. The solvent was evaporated. The resulting solid was dissolved in water and the pH was adjusted to 7. The aqueous solution was extracted with EtOAc and the combined extracts were dried over MgSO₄ and evaporated. To the residue in MeOH was added 1 equivalent of 1N NaOH. The solvent was evaporated to give compound **37** as a brown solid:

¹H NMR (DMSO-d₆) δ 0.82 (d, J = 6.6 Hz, 6 H), 1.20-1.31 (m, 2 H), 1.48-1.54 (m, 1 H), 3.52 (d, J = 3.8 Hz, 2 H), 4.18-4.24 (m, 2 H), 5.57 (s, 2 H), 6.22 (t, J = 4.0 Hz, 1 H), 6.78-6.82 (m, 1 H), 6.89-6.94 (m, 1 H), 7.06-7.28 (m, 4 H), 7.47 (d, J = 7.5 Hz, 1 H), 7.58 (d, J = 8.4 Hz, 1 H);

MS m/e 392 (MH⁺).



38

Compound **38** was prepared using the same procedure as compound **4** with 2-benzimidazolemethanol:

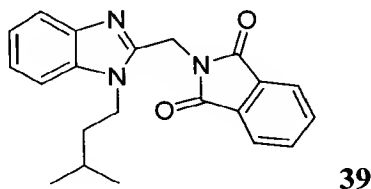
^1H NMR (CDCl_3) δ 0.87 (d, J = 6.5 Hz, 6 H), 1.32-1.40 (m, 2 H), 1.48-1.55 (m, 1 H), 4.14-4.19 (m, 2 H), 4.87 (s, 2 H), 5.72 (s, 2 H), 7.28-7.40 (m, 6 H), 7.72-7.79 (m, 2 H);

IR (KBr, cm^{-1}) 2948, 1473, 1458, 1438, 1400, 1035, 740;

5 MS m/e 349 (MH^+);

Anal. Calcd for $\text{C}_{21}\text{H}_{24}\text{N}_4\text{O} \cdot 0.25 \text{H}_2\text{O}$: C, 71.46; H, 7.00; N, 15.87

Found: C, 71.23; H, 6.99; N, 15.90.



10

Compound **39** was prepared using the same procedure as compound **4** with phthalimide in 26% yield:

^1H NMR (CDCl_3) δ 1.00 (d, J = 6.2 Hz, 6H), 1.67-1.81 (m, 3H), 4.30 (t, J = 7.9

15 Hz, 2H), 5.11 (s, 1H), 7.17-7.32 (m, 4H), 7.68-7.76 (m, 2H), 7.85-7.91 (m, 2H);

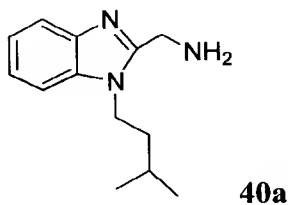
IR (KBr, cm^{-1}) 2953, 1774, 1718, 1469, 1424, 1394, 1323, 1115, 950, 749, 723;

MS m/e 348 (MH^+);

Anal. Calcd for $\text{C}_{21}\text{H}_{21}\text{N}_3\text{O}_2 \cdot 0.5 \text{H}_2\text{O}$: C, 70.77; H, 6.22; N, 11.79

Found: C, 70.76; H, 6.39; N, 11.62.

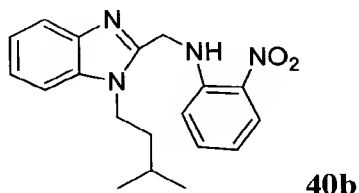
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Compound **39** (2.0 g, 6.00 mmol) was stirred at reflux with excess hydrazine hydrate (617 mg, 17.61 mmol) in EtOH for 2 hours. The reaction mixture was diluted with EtOH and the precipitate was filtered and washed with

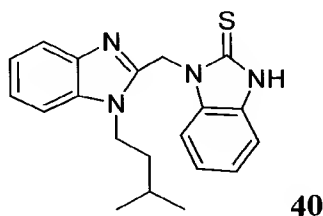
25

EtOH. The filtrate was concentrated, diluted with EtOAc, washed with water and brine, dried over MgSO_4 , and concentrated to give 967 mg (74% yield) of compound **40a** as a brown oil which was used without further purification.



A mixture of amine **40a** (960 mg, 4.42 mmol), 1-fluoro-2-nitrobenzene (811 mg, 5.75 mmol), and K_2CO_3 (732 mg, 5.03 mmol) in CH_3CN was stirred at reflux for 18 hours. The reaction mixture was filtered and washed with EtOAc.

- 10 The filtrate was concentrated, subjected to flash column chromatography (gradient, hexanes/EtOAc, 3:1 to 2:1), and recrystallized from Et_2O /hexanes to give 486 mg (32% yield) of compound **40b** as an orange solid.



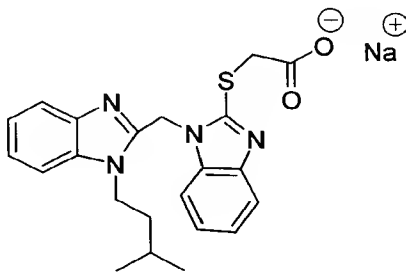
15

Compound **40b** (1.0 g, 2.96 mmol) was reduced under H_2 in a Parr apparatus in the presence of 10% palladium on carbon (150 mg) in a mixture of EtOAc and MeOH (22 mL, 10:1) at 60 psi for 45 minutes. The catalyst was removed by filtration through a pad of celite and the filtrate was concentrated.

- 20 This diamine was then treated with 1,1'-thiocarbonyldiimidazole (686 mg, 3.85 mmol) in THF and stirred at reflux for 5 hours. The solvent was concentrated and the residue was subjected to flash column chromatography (hexanes/EtOAc, 2:1) to give 835 mg (81% yield) of compound **40**:

^1H NMR (CDCl_3) δ 0.91 (d, J = 6.6 Hz, 6H), 1.34-1.42 (m, 2H), 1.64-1.73 (m, 2H), 4.39 (bt, J = 8.0 Hz, 2H), 5.83 (s, 2H), 7.10-7.27 (m, 5H), 7.37 (d, J = 7.4 Hz, 1H), 7.50 (d, J = 7.7 Hz, 1H), 7.57 (d, J = 7.5 Hz, 1H), 13.03 (s, 1H);
MS m/e 351 (MH^+).

5

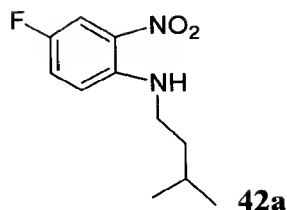


A mixture of compound **40** (150 mg, 0.43 mmol), bromoacetic acid (65 mg, 0.47 mmol) and K_2CO_3 (65 mg, 0.47 mmol) in CH_3CN (2 mL) were stirred at room temperature for 3 days. Additional bromoacetic acid (60 mg, 0.43 mmol) in CH_3CN (2 mL) was added and the reaction mixture was refluxed for 4 hours. The solvent was evaporated. The residue was diluted with saturated aqueous NaHCO_3 and extracted with EtOAc. The aqueous layer was then neutralized to pH 7 and extracted with EtOAc. The extracts were dried over MgSO_4 and evaporated to give 77 mg (44% yield) of compound **41** as a pale brown solid.

A mixture of acid **41** (125 mg, 0.31 mmol) and 1N NaOH (0.31 mL, 0.31 mmol) in MeOH (3 mL) was stirred at room temperature and was evaporated to give a light green product. This material was dissolved in water, treated with active carbon and filtered. The filtrate was concentrated to give 107 mg (80% yield) of the sodium salt of compound **41**:

^1H NMR ($\text{DMSO}-d_6$) δ 0.85 (d, J = 6.6 Hz, 6 H), 1.23-1.33 (m, 2 H), 1.51-1.60 (m, 2 H), 3.82 (s, 2 H), 4.22-4.28 (m, 2 H), 5.72 (s, 2 H), 7.03-7.26 (m, 4 H), 7.36 (d, J = 7.0 Hz, 1 H), 7.48-7.57 (m, 3 H);
MS m/e 409 (MH^+).

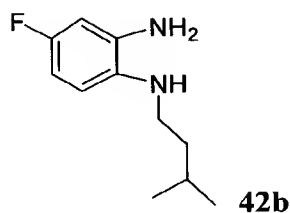
67



To a solution of 2,5-difluoronitrobenzene (45 g, 282.86 mmol) in CH₃CN (500 mL) was added potassium carbonate (78 g, 565.72 mmol) and isoamylamine (25 g, 282.86 mmol). The reaction mixture was stirred at room temperature for 18 hours with the aid of a mechanical stirrer. The potassium carbonate was filtered and the filtrate was evaporated to give an orange oil. The oil was diluted with EtOAc, washed with water and brine, dried over MgSO₄, and evaporated. Purification by flash column chromatography (hexanes/EtOAc, 20:1) gave 53 g (83% yield) of compound **42a**:

¹H NMR (CDCl₃) δ 0.98 (d, J = 6.5 Hz, 6H), 1.61-1.65 (m, 2H), 1.74-1.78 (m, 1H), 3.30 (t, J = 7.3 Hz, 2H), 6.83 (dd, J = 4.6, 9.5 Hz, 1H), 7.23-7.27 (m, 1H), 7.85 (dd, J = 3.1, 9.2 Hz, 1H);

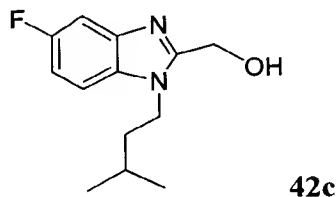
MS m/e 226 (MH⁺).



To a solution of compound **42a** (53 g, 235.14 mmol) and concentrated HCl (15 mL) in MeOH (200 mL) was added 10% palladium on carbon (5 g) and the mixture was reduced under H₂ at 55 psi for 1.5 hours. The catalyst was removed by filtration through a pad of celite and the filtrate was concentrated to give 47 g (87% yield) of diamine **42b** as the HCl salt:

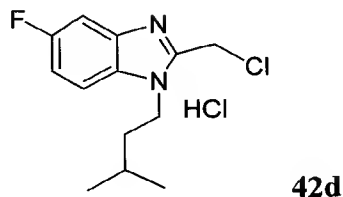
^1H NMR (CDCl_3) δ 0.97 (d, J = 6.2 Hz, 6 H), 1.65-1.77 (m, 3 H), 3.36 (t, J = 8.0 Hz, 2 H), 6.50-6.57 (m, 1 H), 6.71 (dd, J = 2.7, 10.5 Hz, 1 H), 7.28 (dd, J = 5.5, 8.8 Hz, 1 H);
MS m/e 197 (MH^+).

5



A mixture of diamine **42b** (47 g, 200.66 mmol) and glycolic acid (16 g, 210.70 mmol) in 4N HCl (500 mL) were stirred at reflux for 18 hours. The
10 reaction mixture was cooled to 0 °C and was adjusted to pH 8 by adding concentrated ammonium hydroxide. The product was extracted with EtOAc, dried over MgSO_4 , and evaporated. The crude product was recrystallized with EtOAc/hexanes to give 27 g (37% yield) of compound **42c** as brown crystals:

15 ^1H NMR (CDCl_3) δ 1.02 (d, J = 6.0 Hz, 6 H), 1.68-1.75 (m, 3 H), 3.19 (bs, 1 H), 4.22 (t, J = 7.7 Hz, 2 H), 4.93 (s, 2 H), 7.06 (dt, J = 2.2, 9.1 Hz, 1 H), 7.26-7.28 (m, 1 H), 7.37 (dd, J = 2.1, 8.9 Hz, 1 H);
MS m/e 237 (MH^+).



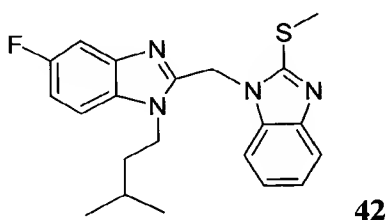
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To a solution of alcohol **42c** (27 g, 112.99 mmol) in CH_2Cl_2 (100 mL) was slowly added thionyl chloride (27g, 225.99 mmol) and the reaction mixture was stirred at 65 °C for 2.5 hours. The solvent and excess thionyl chloride were
25 evaporated to give a grey solid. The solid was suspended in Et_2O and evaporated

several times to ensure removal of the solvent and reagent. The solid was then dissolved in a minimal amount of CH_2Cl_2 and precipitated by addition of hexanes. The solid was collected by filtration and triturated with Et_2O to give 32 g (96% yield) of compound **42d** as a grey solid:

5

^1H NMR (CDCl_3) δ 1.08 (d, J = 6.4 Hz, 6H), 1.79-1.90 (m, 3H), 4.44 (bt, J = 8.2 Hz, 2H), 5.32 (s, 2H), 7.36 (dt, J = 2.2, 8.9, 1H), 7.54-7.59 (m, 2H);
MS m/e 255 (MH^+).

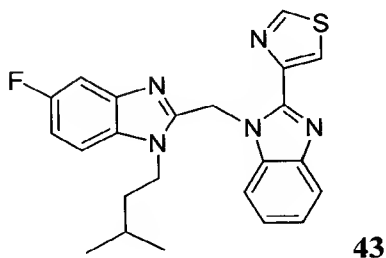


10

Compound **42** was prepared using the same procedure as compound **4** with compound **42d** and 2-(methylmercapto)benzimidazole in 95% yield:

15 ^1H NMR (CD_3OD) δ 0.99 (d, J = 6.5 Hz, 6 H), 1.61-1.66 (m, 2 H), 1.66-1.71 (m, 1 H), 2.91 (s, 3 H), 4.40-4.43 (m, 2 H), 6.05 (s, 2 H), 7.21 (td, J = 2.4, 9.2 Hz, 1 H), 7.27 (dd, J = 2.4, 8.9 Hz, 1 H), 7.43-7.51 (m, 2 H), 7.63-7.65 (m, 2 H), 7.76 (d, J = 7.8 Hz, 1 H);
MS m/e 384 (MH^+).

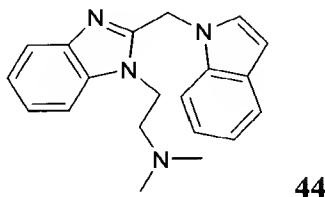
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Compound **43** was prepared using the same procedure as compound **4** with compound **42d** and thiabenazole in 67% yield:

^1H NMR (CD_3OD) δ 1.02 (d, J = 6.2 Hz, 6 H), 1.72-1.74 (m, 3 H), 4.45-4.48 (m, 2 H), 6.56 (s, 2 H), 7.17-7.21 (m, 2 H), 7.46-7.53 (m, 2 H), 7.62-7.64 (m, 1 H), 7.72 (d, J = 8.1 Hz, 1 H), 7.84 (d, J = 7.8 Hz, 1 H), 8.61 (s, 1 H), 9.09 (s, 1 H); MS m/e 420 (MH^+).

5



Compound **44** was prepared using the same procedure sequence as compound **1** starting with indole:

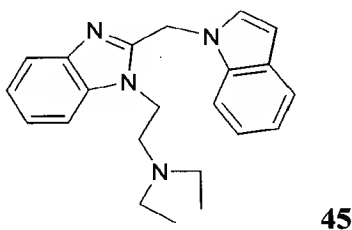
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^1H NMR (CDCl_3) δ 2.01 (bs, 8 H), 4.02 (t, J = 7.3 Hz, 2 H), 5.64 (s, 2 H), 6.55 (dd, J = 0.8, 3.2 Hz, 1 H), 7.08-7.29 (m, 6 H), 7.48 (d, J = 8.6 Hz, 1 H), 7.62 (d, J = 7.5 Hz, 1 H), 7.80-7.84 (m, 1 H);

IR (KBr, cm^{-1}) 2943, 2824, 1613, 1463, 1420, 1323, 741;

15

MS m/e 319 (MH^+).



Compound **45** was prepared using the same procedure sequence as compound **1** starting with indole and 2-chloro- N,N -diethylethylamine hydrochloride:

20

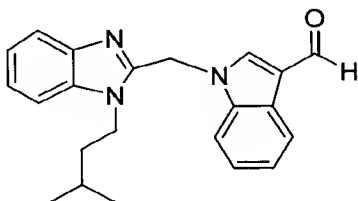
^1H NMR (CD_3OD) δ 1.31 (t, J = 7.3 Hz, 6 H), 3.10 (t, J = 8.1 Hz, 2H), 3.60-3.75 (m, 4 H), 4.94 (s, 2 H), 4.99-5.04 (m, 2 H), 6.75 (d, J = 8.0 Hz, 1 H), 6.81 (t, J =

7.5 Hz, 1 H), 7.10 (t, $J = 7.4$ Hz, 1 H), 7.19 (d, $J = 7.2$ Hz, 1 H), 7.62-7.72 (m, 4 H), 7.82 (d, $J = 7.2$ Hz, 1 H), 8.06 (d, $J = 7.4$ Hz, 1 H);

IR (KBr, cm^{-1}) 3396, 2925, 1728, 1606, 1523, 1464, 1253, 1136, 753;

MS m/e 349 (MH^+).

5



46

To a suspension of indole-3-carboxaldehyde (129 mg, 0.89 mmol) in CH_3CN was added NaH (60% suspension in mineral oil, 39 mg, 0.98 mmol).

- 10 After stirring for 15 minutes, the neutral form of compound **4c** (232 mg, 0.98 mmol) was added. The reaction mixture was stirred at room temperature for 2.5 hours and then heated to 70 °C for 1.5 hours. After evaporation of the solvent, the resulting residue was diluted with aqueous saturated NaHCO_3 and extracted with EtOAc. The organic extracts were dried over MgSO_4 and evaporated.
- 15 Column chromatography (gradient, hexanes/EtOAc, 1:1 to EtOAc/hexanes, 2:1) gave 199 mg (65% yield) of compound **46**:

^1H NMR (CDCl_3) δ 0.68 (d, $J = 6.6$ Hz, 6 H), 1.05-1.13 (m, 2 H), 1.23-1.36 (m, 1 H), 3.87-3.93 (m, 2 H), 5.60 (s, 2 H), 7.22-7.33 (m, 4 H), 7.47-7.54 (m, 1 H), 7.70 (s, 1 H), 7.75-7.80 (m, 1 H), 8.23-8.27 (m, 1 H), 9.90 (s, 1 H);

20

IR (KBr, cm^{-1}) 3432, 2961, 1662, 1651, 1526, 1463, 1386, 1189, 1171, 1038, 778, 739;

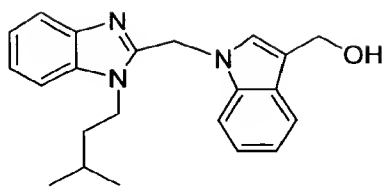
MS m/e 346 (MH^+);

Anal. Calcd for $\text{C}_{22}\text{H}_{23}\text{N}_3\text{O} \cdot 0.25 \text{H}_2\text{O}$: C, 75.51; H, 6.77; N, 12.01

25

Found: C, 75.60; H, 6.59; N, 11.83.

72

**47**

Sodium borohydride (10 mg, 0.26 mmol) was added to a solution of aldehyde **46** (70 mg, 0.20 mmol) in MeOH (5 mL) at 0 °C. The reaction was monitored by thin layer chromatography and when complete, the solvent was evaporated. The resulting residue was subjected to flash column chromatography (straight EtOAc) to give 50 mg (70% yield) of compound **47** as a white solid:

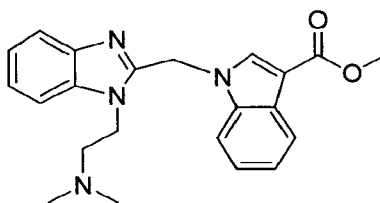
^1H NMR (CDCl_3) δ 0.71 (d, J = 6.6 Hz, 6 H), 1.04-1.12 (m, 2 H), 1.22-1.33 (m, 1 H), 3.87-3.92 (m, 2 H), 4.82 (s, 2 H), 5.56 (s, 2 H), 7.12 (s, 1 H), 7.14-7.31 (m, 5 H), 7.47 (d, J = 8.2 Hz, 1 H), 7.71-7.74 (m, 1 H), 7.80-7.83 (m, 1 H);

IR (KBr, cm^{-1}) 3247, 2950, 2867, 1612, 1465, 1309, 1038, 743;

MS m/e 348 (MH^+);

Anal. Calcd for $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O} \cdot 0.25 \text{ H}_2\text{O}$: C, 75.08; H, 7.30; N, 11.94

Found: C, 74.86; H, 7.17; N, 11.82.

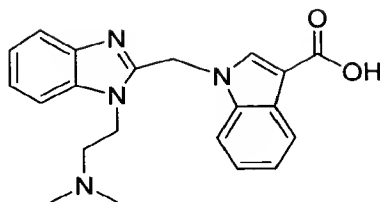
**48**

Compound **48** was prepared using the same procedure sequence as compound **1** starting with methyl indole-4-carboxylate:

^1H NMR (CDCl_3) δ 2.00 (s, 6 H), 2.13 (t, J = 6.9 Hz, 2 H), 3.81 (s, 3 H), 4.00 (t, J = 6.9 Hz, 2 H), 5.63 (s, 2 H), 7.21-7.26 (m, 5 H), 7.50 (dd, J = 2.4, 5.9 Hz, 1 H), 7.76 (dd, J = 4.5, 7.5 Hz, 1 H), 7.79 (s, 1 H), 8.13 (dd, J = 0.3, 6.2 Hz, 1 H);

MS m/e 377 (MH^+).

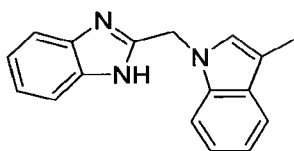
73



49

A mixture of methyl ester **48** (45 mg, 0.12 mmol) and sodium hydroxide (480 mg, 12.00 mmol) in MeOH (15 mL) was stirred at room temperature for 2 hours and then heated at reflux for 4 days. The solution was neutralized with 1N HCl and the solvent was evaporated. The product was dissolved in cold MeOH and decanted from the solids. The solvent was evaporated to give compound **49**:

^1H NMR (CD_3OD) δ 2.93 (s, 6 H), 3.30-3.34 (m, 2 H), 4.87-4.92 (m, 2 H), 6.16 (s, 2 H), 7.27-7.30 (m, 2 H), 7.42-7.54 (m, 2 H), 4.63 (dd, $J = 3.0, 6.8$ Hz, 1 H), 7.67 (d, $J = 7.5$ Hz, 1 H), 7.89 (d, $J = 6.4$ Hz, 1 H), 8.17-8.20 (m, 1 H), 8.23 (s, 1 H);
MS m/e 361 (MH^+).

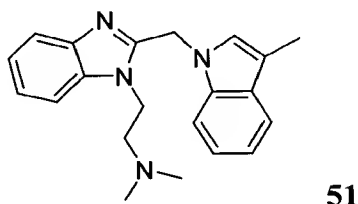


50

To a solution of 3-methylindole (390 mg, 2.97 mmol) in CH_3CN was added NaH (60% suspension in mineral oil, 72 mg, 2.97 mmol) and the mixture was stirred at room temperature for 1 hour. Compound **1b** was added and the mixture was stirred at room temperature for 17 hours. The solvent was evaporated and the residue was diluted with CH_2Cl_2 , washed with water, dried over MgSO_4 , and concentrated. Purification by flash column chromatography (hexanes/EtOAc, 4:1) gave the mesyl protected intermediate.

The mesyl protecting group was removed by stirring the mesyl protected intermediate (25 mg, 0.07 mmol) with excess hydrazine hydrate (2 mL) in MeOH

(5 mL) at reflux. The solvent was evaporated and the residue was diluted with CH_2Cl_2 , washed with water, dried over MgSO_4 , and concentrated. Intermediate **50** was used without further purification.

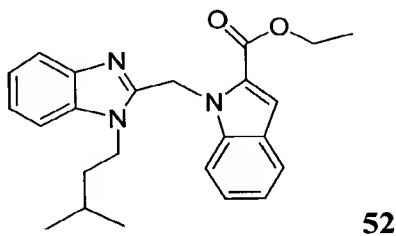


To a mixture of **50** (10 mg, 0.04 mmol) and NaH (60% suspension in mineral oil, 4 mg, 0.1 mmol) in THF (1 mL) was added 2-chloro-N,N-dimethylethylamine hydrochloride (6 mg, 0.04 mmol) and the mixture was stirred at reflux for 24 hours. The solvent was evaporated and the residue was diluted with CH_2Cl_2 , washed with water, dried over MgSO_4 , and concentrated. Purification by flash column chromatography (straight EtOAc) gave 6 mg (46% yield) of compound **51**:

10

^1H NMR (CDCl_3) δ 2.00 (s over t, $J = 7.5$ Hz, 8 H), 2.27 (s, 3 H), 4.01-4.06 (t, $J = 7.5$ Hz, 2 H), 5.57 (s, 2 H), 6.89 (s, 1 H), 6.89-7.32 (m, 5 H), 7.44 (d, $J = 8.9$ Hz, 1 H), 7.56 (d, $J = 8.7$ Hz, 1 H), 7.80-7.83 (m, 1 H); MS m/e 333 (MH^+).

15

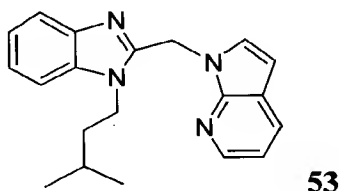


Compound **52** was prepared using the same procedure as compound **4** with compound **4c** and ethyl indole-2-carboxylate:

^1H NMR (CDCl_3) δ 0.80 (d, J = 6.6 Hz, 6 H), 1.02-1.09 (m, 3 H), 1.41 (t, J = 7.1 Hz, 3 H), 4.02-4.07 (m, 2 H), 4.39 (q, J = 7.1 Hz, 2 H), 6.30 (s, 2 H), 7.11 (t, J = 7.1 Hz, 1 H), 7.19-7.25 (m, 4 H), 7.44 (s, 1 H), 7.60-7.66 (m, 2 H), 7.76-7.80 (m, 1 H);

5 IR (KBr, cm^{-1}) 2956, 2871, 1699, 1519, 1458, 1325, 1257, 1194, 1139, 1096, 743;

MS m/e 390 (MH^+).

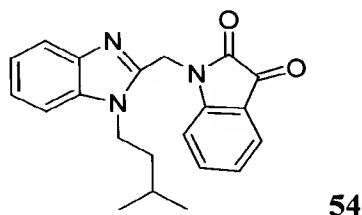


10

Compound **53** was prepared using the same procedure as compound **4** with compound **4c** and 7-azaindole:

15 ^1H NMR (CDCl_3) δ 0.57 (d, J = 6.6 Hz, 6 H), 0.86-0.97 (m, 2 H), 1.04-1.13 (m, 1 H), 3.99-4.05 (m, 2 H), 5.77 (s, 2 H), 6.41 (d, J = 3.6 Hz, 1 H), 7.05 (dd, J = 4.7, 7.8 Hz, 1 H), 7.19-7.25 (m, 4 H), 7.33-7.76 (m, 1 H), 7.86 (dd, J = 1.6, 7.8 Hz, 1 H), 8.31 (dd, J = 1.4, 4.7 Hz, 1 H);

MS m/e 319 (MH^+).

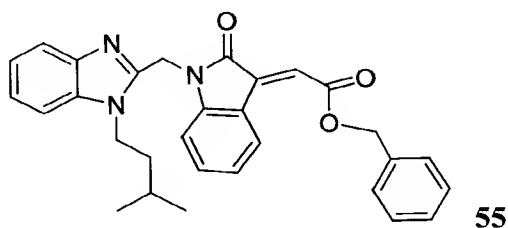


20

To a solution of isatin (7.35 g, 50.0 mmol) in DMF (250 ml) at 0 °C was added NaH (5.0 g, 60% dispersion, 125 mmol). The resulting mixture was stirred at 0 °C for 30 minutes and then chloride **4c** (13.0 g, 55.0 mmol) was added. After
25 stirring for additional 2 hours, the mixture was diluted with EtOAc (250 ml),

washed with saturated NH_4Cl and water (250 ml x 2), brine, dried over MgSO_4 , and concentrated. The residue was purified by flash chromatography (gradient, hexane:EtOAc = 3:1 to 1:2) to give 11.6 g (67% yield) of compound **54** as an orange solid:

- 5 ^1H NMR (CD_3OD) δ 0.96 (d, J = 6.6 Hz, 6 H), 1.54-1.57 (m, 2 H), 1.65-1.75 (m, 1 H), 4.21-4.26 (m, 2 H), 5.24 (s, 2 H), 7.10-7.11 (m, 1 H), 7.26-7.32 (m, 3 H), 7.54-7.59 (m, 3 H), 7.76-7.78 (m, 1 H);
MS m/e 348 (MH^+).



10

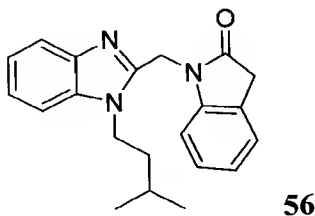
The isatin compound **54** (416 mg, 1.20 mmol) and benzyl (triphenylphosphoranylidene) acetate (540 mg, 1.32 mmol) were stirred in CH_2Cl_2 for 1 hour. The solvent was evaporated and column chromatography (20% EtOAc in hexanes) gave 350 mg (60% yield) of compound **55**:

15

^1H NMR (CDCl_3) δ 0.91 (d, J = 6.6 Hz, 6 H), 1.39-1.47 (m, 2 H), 1.59-1.73 (m, 2 H), 4.19-4.24 (m, 2 H), 5.29 (s, 2 H), 5.31 (s, 2 H), 6.99-7.04 (m, 2 H), 7.25-7.32 (m, 4 H), 7.35-7.43 (m, 6 H), 7.27-7.80 (m, 1 H), 8.50 (d, J = 7.5 Hz, 1 H);

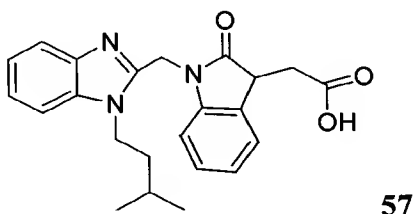
20

MS m/e 480 (MH^+).



Compound **55** (100 mg, 0.21 mmol) was treated with hydrazine (13 mg, 0.42 mmol) in ethanol (5 mL) and heated at 60 °C for 16 hours. Solvent was evaporated and column chromatography (10% EtOAc in hexanes) gave compound **56** as a white solid:

^1H NMR (CDCl_3) δ 0.97 (d, J = 6.5 Hz, 6 H), 1.45-1.52 (m, 2 H), 1.65-1.76 (m, 1 H), 3.59 (s, 2 H), 4.23-4.29 (m, 2 H), 5.27 (s, 2 H), 7.01 (t, J = 7.0 Hz, 1 H), 7.18-7.33 (m, 5 H), 7.41 (d, J = 7.9 Hz, 1 H), 7.76-7.80 (m, 1 H);
MS m/e 334 (MH^+).

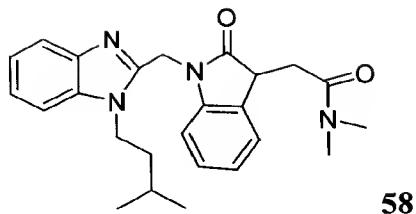


To a solution of compound **55** (100 mg, 0.21 mmol) in EtOAc (7 mL) was added 10% palladium on carbon (25 mg). The solution was agitated under H_2 at 50 psi for 3 hours. The reaction mixture was diluted with MeOH and the catalyst was filtered through a pad of celite. The filtrate was concentrated and the residue was washed with EtOAc to give 60 mg (73 % yield) of compound **57** as a light green solid:

^1H NMR (CDCl_3) δ 0.94 (d, J = 6.5 Hz, 6 H), 1.46-1.70 (m, 3 H), 2.81 (dd, J = 6.8, 17.0 Hz, 1 H), 2.97 (dd, J = 4.8, 17.0 Hz, 1 H), 3.81 (t, J = 5.6 Hz, 1 H), 4.25-4.30 (m, 2 H), 5.09 (d, J = 16.0 Hz, 1 H), 5.24 (d, J = 16.0 Hz, 1 H), 6.95-7.01 (m, 1 H), 7.06-7.25 (m, 4 H), 7.29 (d, J = 7.2 Hz, 1 H), 7.49 (d, J = 7.7 Hz, 1 H), 7.59 (d, J = 7.6 Hz, 1 H), 12.41 (s, 1 H);

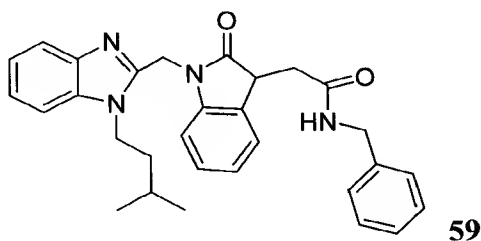
MS m/e 392 (MH^+).

78



Acid **57** (120 mg, 0.31 mmol), dimethyl amine hydrochloride (25 mg, 0.31 mmol), HOBT (46 mg, 0.34 mmol), N-methylmorpholine (85 mg, 0.84 mmol), and EDAC (65 mg, 0.34 mmol) were stirred in anhydrous DMF (1 mL) for 16 hours at room temperature. The reaction mixture was diluted with EtOAc and water. An insoluble white solid was filtered and triturated in EtOAc to give compound **58**:

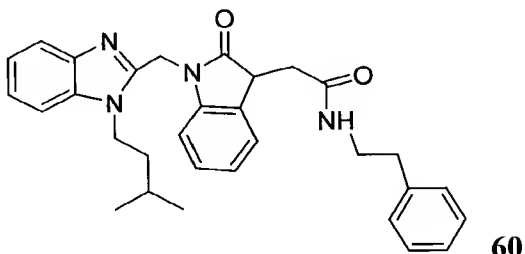
- ¹H NMR (CDCl₃) δ 0.96 (d, J = 6.4 Hz, 3 H), 0.98 (d, J = 6.4 Hz, 3 H), 1.41-1.76 (m, 3 H), 2.75 (dd, J = 9.0, 16.5 Hz, 1 H), 2.98 (s, 3 H), 2.99 (s, 3 H), 3.16 (dd, J = 3.1, 16.6 Hz, 1 H), 4.01 (dd, J = 3.0, 9.0 Hz, 1 H), 4.27 (t, J = 8.2 Hz, 2 H), 5.08 (d, J = 15.4 Hz, 1 H), 5.42 (d, J = 15.4 Hz, 1 H), 6.95-7.00 (m, 1 H), 7.16-7.32 (m, 5 H), 7.41 (d, J = 7.8 Hz, 1 H), 7.74-7.78 (m, 1 H);
- MS m/e 419 (MH⁺).



- Compound **59** was prepared using the same procedure as compound **58** with benzyl amine:

¹H NMR (CDCl₃) δ 0.96 (d, J = 6.4 Hz, 3 H), 0.98 (d, J = 6.4 Hz, 3 H), 1.42-1.75 (m, 3 H), 2.70 (dd, J = 7.2, 15.4 Hz, 1 H), 3.02 (dd, J = 5.7, 15.4 Hz, 1 H), 3.95 (t, J = 6.3 Hz, 1 H), 4.28 (t, J = 8.1 Hz, 2 H), 4.45 (t, J = 5.0 Hz, 2 H), 5.11 (d, J =

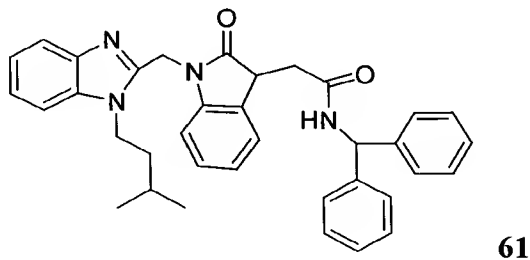
15.4 Hz, 1 H), 5.42 (d, $J = 15.4$ Hz, 1 H), 6.49-6.61 (m, 1 H), 6.94-7.02 (m, 1 H), 7.21-7.33 (m, 10 H), 7.44 (d, $J = 7.9$ Hz, 1 H), 7.74-7.66 (m, 1 H);
MS m/e 481 (MH^+).



5

Compound **60** was prepared using the same procedure as compound **58** with phenethylamine:

- 10 1H NMR ($CDCl_3$) δ 0.97 (d, $J = 6.5$ Hz, 6 H), 1.40-1.93 (m, 3 H), 2.51 (q, $J = 7.9$ Hz, 1 H), 2.78-2.96 (m, 3 H), 3.50-3.62 (m, 2 H), 3.91-3.96 (m, 1 H), 4.24 (t, $J = 8.1$ Hz, 2 H), 5.04 (d, $J = 15.4$ Hz, 1 H), 5.35 (d, $J = 15.4$ Hz, 1 H), 6.07 (t, $J = 5.6$ Hz, 1 H), 7.00 (t, $J = 7.5$ Hz, 1 H), 7.15-7.32 (m, 10 H), 7.40 (d, $J = 7.6$ Hz, 1 H), 7.72-7.77 (m, 1 H);
- 15 MS m/e 495 (MH^+).



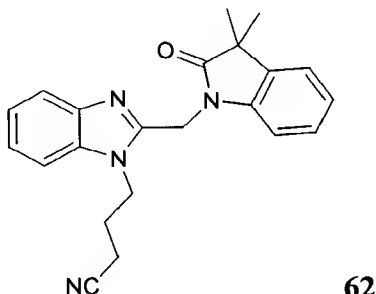
- 20 Compound **61** was prepared using the same procedure as compound **58** with aminodiphenylmethane:

1H NMR ($CDCl_3$) δ 0.94 (d, $J = 6.4$ Hz, 3 H), 0.96 (d, $J = 6.4$ Hz, 3 H), 1.39-1.71 (m, 3 H), 2.70 (dd, $J = 7.1, 15.4$ Hz, 1 H), 3.03 (dd, $J = 6.2, 15.4$ Hz, 1 H), 3.97 (t,

$J = 6.6$ Hz, 1 H), 4.22 (t, $J = 8.2$ Hz, 1 H), 5.03 (d, $J = 15.4$ Hz, 1 H), 5.34 (d, $J = 15.4$ Hz, 1 H), 6.27 (d, $J = 8.0$ Hz, 1 H), 6.90-7.05 (m, 2 H), 7.15-7.36 (m, 14 H), 7.41 (d, $J = 7.8$ Hz, 1 H), 7.72-7.77 (m, 1 H);

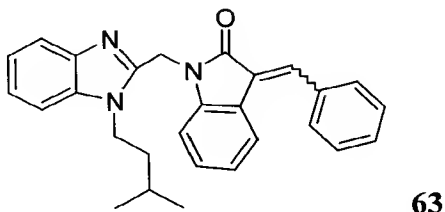
MS m/e 557 (MH^+).

5



To a solution of 1,3-dihydro-3,3-dimethyl-2H-indol-2-one (100 mg, 0.62 mmol) in THF (20 mL) was added BTPP (0.61 g, 1.98 mmol). The solution was stirred for 15 minutes and then the compound **25b** (168 mg, 0.61 mmol) was added and the mixture was stirred for 3 days at room temperature. The solvent was removed and the residue was washed with water. (20 mL, 10x) to give 110 mg (50% yield) of compound **62** as a clear glass:

1H NMR (DMSO- d_6) δ 1.41 (s, 6 H), 2.05-2.08 (m, 2 H), 2.48 (t, $J = 4.3$ Hz, 2 H), 4.25-4.56 (m, 2 H), 5.25 (s, 2 H), 7.07 (t, $J = 4.47$ Hz, 1 H), 7.18-7.39 (m, 4 H), 7.55 (d, $J = 4.7$ Hz, 2 H), 7.81 (d, $J = 4.1$ Hz, 1 H);
MS m/e 357 (MH^+).

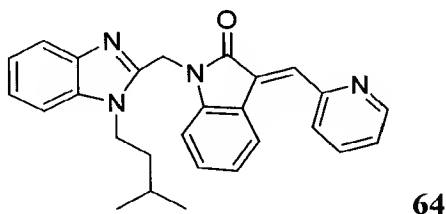


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To a solution of benzyltriphenylphosphonium chloride (129 mg, 0.33 mmol) in CH_2Cl_2 was added NaH (16 mg, 0.39 mmol) and the mixture was

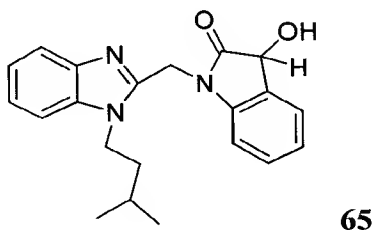
stirred for 30 minutes. This solution was added dropwise to a solution of the isatin compound **54** in CH_2Cl_2 . The reaction mixture was allowed to stir for 1 hour, was diluted with EtOAc, and washed with H_2O . The organic layer was dried over MgSO_4 and evaporated. Column chromatography (20% EtOAc in hexanes) gave compound **63** as a 2:1 mixture of regioisomers:

^1H NMR (CDCl_3) δ 0.82, 0.93 (d, J = 6.6 Hz, 6 H), 1.32-1.46 (m, 2 H), 1.53-1.77 (m, 1 H), 4.20-4.31 (m, 2 H), 6.85, 7.03 (td, J = 1.0, 7.7 Hz, 1 H), 7.15-7.21 (m, 1 H), 7.25-7.39 (m, 4 H), 7.43-7.50 (m, 3 H), 7.63 (bs, 1 H), 7.60, 7.93 (s, 1 H), 7.62-7.66, 8.29-8.33 (m, 1 H);
MS m/e 422 (MH^+).



Compound **64** was prepared using the same procedure as compound **63** with triphenyl(2-pyridylmethyl)-phosphonium chloride hydrochloride:

^1H NMR (CDCl_3) δ 0.89 (d, J = 6.6 Hz, 6 H), 1.39-1.47 (m, 2 H), 1.64-1.73 (m, 1 H), 4.25-4.31 (m, 2 H), 5.38 (s, 2 H), 7.03 (t, J = 7.2 Hz, 1 H), 7.22-7.41 (m, 6 H), 7.63 (d, J = 7.8 Hz, 1 H), 7.78-7.83 (m, 3 H), 8.86 (d, J = 3.7 Hz, 1 H), 9.02 (d, J = 7.5 Hz, 1 H);
MS m/e 423 (MH^+).



To a solution of compound **54** (102 mg, 0.29 mmol) in MeOH (5 mL) was added 10% palladium on carbon (20 mg) and the mixture was aggitated on a Parr apparatus under H₂ at 50 psi for 18 hours. The catalyst was filtered through a pad of celite and the filtrate was evaporated. The residue was triturated in a mixture
5 of Et₂O and hexanes and then filtered to give 70 mg (69% yield) of compound **65**:

¹H NMR (CDCl₃) δ 0.98 (d, J = 6.6 Hz, 6 H), 1.48-1.76 (m, 3 H), 3.28 (bs, 1 H), 4.19-4.25 (m, 2 H), 5.10 (s, 1 H), 5.13 (d, J = 15.5 Hz, 1 H), 5.22 (d, J = 15.5 Hz, 1 H), 7.07 (t, J = 7.0 Hz, 1 H), 7.23-7.30 (m, 4 H), 7.35 (d, J = 7.7 Hz, 1 H), 7.42
10 (d, J = 7.4 Hz, 1 H), 7.73-7.77 (m, 1 H);

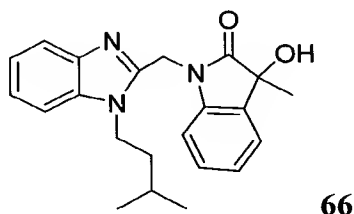
IR (KBr, cm⁻¹) 3423, 2956, 1720, 1615, 1468, 1369, 1172, 743;

MS m/e 378 (MH⁺);

Anal. Calcd for C₂₁H₂₄N₃O₂: C, 71.98; H, 6.90; N, 11.99

Found: C, 71.67; H, 6.57; N, 11.66.

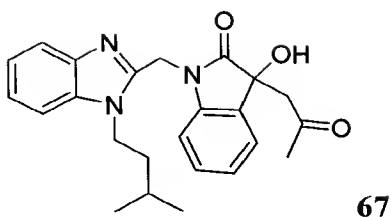
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To a round bottom flask charged with methyl lithium in ether (1.4 M, 1.18 mL, 1.65 mmol) was added ZnCl₂ in ether (1.0 M, 1.27 mL, 1.27 mmol) at –
20 78°C. The mixture was allowed to stir for 1 hour. Compound **54** (442 mg, 1.27 mmol) was added and the mixture was stirred at –78 °C for 1 hour. The temperature was raised to 21 °C. Column chromatography (gradient, 15 – 20 % EtOAc in hexanes) gave compound **66** as a yellow solid:

25 ¹H NMR (CDCl₃) δ 1.05 (d, J = 6.2 Hz, 6 H), 1.65 (s, 3 H), 1.69-1.82 (m, 3 H), 4.19-4.30 (m, 2 H), 4.88 (d, J = 16.4 Hz, 1H), 5.44 (d, J = 16.4 Hz, 1 H), 6.90 (d, J = 7.8 Hz, 1 H), 7.09 (t, J = 7.5 1 H), 7.18-7.37 (m, 4 H), 7.46 (dd, J = 1.0, 7.3 Hz, 1 H), 7.62 (d, J = 7.1 Hz, 1 H).

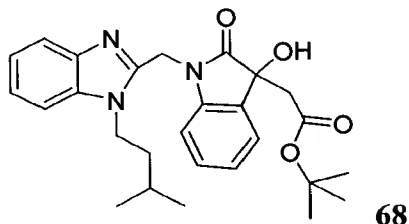
MS m/e 364 (MH⁺).



5 A mixture of compound **54** (200 mg, 0.58 mmol) and K₂CO₃ (1.5 g, 10.85 mmol) in acetone were stirred at reflux for 30 minutes. The solvent was evaporated and the residue was taken up in EtOAc. Column chromatography (gradient, 30-50% EtOAc in hexanes) gave compound **67** as a yellow solid:

10 ¹H NMR (CDCl₃) δ 0.98 (t, J = 6.2 Hz, 6 H), 1.53-1.77 (m, 3 H), 2.15 (s, 3 H), 3.06 (d, J = 17.2 Hz, 1 H), 3.25 (d, J = 17.2 Hz, 1 H), 4.19 (t, J = 8.1 Hz, 2 H), 4.98 (d, J = 15.7 Hz, 1 H), 5.26 (d, J = 15.7 Hz, 1 H), 7.00 (dt, J = 1.4, 7.3 Hz, 1 H), 7.18-7.32 (m, 6 H), 7.67-7.71 (m, 1 H);
MS m/e 406 (MH⁺).

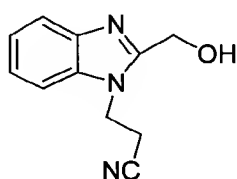
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A mixture of lithium (30% dispersion in mineral oil, 0.5% sodium, 27 mg, 1.17 mmol) and ZnCl₂ (1 M, 0.58 mL, 0.58 mmol) were stirred at 0°C for 15
20 minutes. To this solution, *t*-butyl bromoacetate (76 mg, 0.39 mmol) was added and the resulting mixture was stirred for 15 minutes followed by addition of compound **54** (135 mg, 0.39 mmol) in THF. The mixture was stirred for an additional 15 minutes. The reaction was quenched with 1 N HCl and extracted

with EtOAc. Column chromatography (20 % EtOAc in hexanes) gave compound **68** as a brown solid:

¹H NMR (CDCl₃) δ 0.99 (t, J = 6.4 Hz, 6 H), 1.35 (s, 9 H), 1.55-1.64 (m, 2 H),
 5 1.68-1.79 (m, 1 H), 2.86 (d, J = 15.6 Hz, 1 H), 2.94 (d, J = 15.6 Hz, 1 H), 4.17-
 4.30 (m, 2 H), 5.04 (d, J = 15.6 Hz, 1 H), 5.34 (d, J = 15.6 Hz, 1 H), 7.05 (td, J =
 0.8, 7.5 Hz, 1 H), 7.23-7.39 (m, 6 H), 7.74-7.78 (m, 1 H);
 MS m/e 464 (MH⁺).

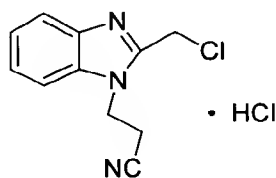
**69a**

Compound **69a** was prepared using Michael addition conditions described by Popov, I. I. (*Khim Geterotskl. Soedin.* **1996** (6), 781-792):

¹H NMR (CDCl₃) δ 3.08 (t, J = 6.8 Hz, 2 H), 4.63 (t, J = 6.8 Hz, 2 H), 4.77 (d, J
 15 = 5.7 Hz, 2 H), 5.73 (t, J = 5.7 Hz, 1 H), 7.17-7.28 (m, 2 H), 7.64 (d, J = 1.2 Hz, 1
 H), 7.70 (d, J = 1.2 Hz, 1 H);
 MS m/e 202 (MH⁺);

Anal. Calcd for C₁₁H₁₁N₃O: C 65.66; H, 5.51; N, 20.88

20 Found: C, 65.94; H, 5.57; N, 21.08.

**69b**

To a solution of alcohol **69a** (20g, 99.4 mmol) in CH₂Cl₂ (50 mL) was slowly
 25 added thionyl chloride (15.4 g, 129.2 mmol). The solution was stirred at room
 temperature for 3 hours. The solvent was evaporated. The residue was diluted with

water and neutralized with saturated aqueous sodium bicarbonate solution, and extracted with EtOAc. The combined extracts were washed with water, dried over MgSO_4 , and evaporated. The residue was triturated with Et_2O and hexane to give 19.78 g (91% yield) of compound **69b** as a white solid:

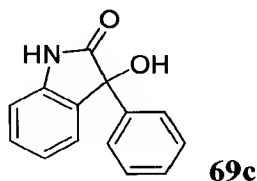
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^1H NMR (CDCl_3) δ 3.02 (t, $J = 7.0\text{ Hz}$, 2 H), 4.65 (t, $J = 7.0\text{ Hz}$, 2 H), 4.99 (s, 2 H), 7.34-7.44 (m, 3 H), 7.79-7.82 (m, 1 H);

MS m/e 220 (MH^+);

Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{ClN}_3$: C, 60.09; H, 4.65; N, 19.13

10 Found: C, 60.09; H, 4.65; N, 19.11.



To a solution of isatin (2.94 g, 20.00 mmol) in THF (50 mL) was slowly
15 added phenyllithium (1.8 M in hexanes, 33 mL, 60.00 mmol) at 0°C . The
resulting solution was stirred at room temperature for 1 hour. The reaction was
quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The
combined extracts were dried over MgSO_4 and concentrated. Purification of the
crude product by flash column chromatography (gradient, hexanes:EtOAc = 2:1
20 to straight EtOAc) gave 3.55 g (79% yield) of compound **69c**:

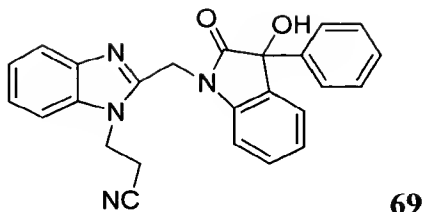
^1H NMR (CDCl_3) δ 6.96 (d, $J = 8.1\text{ Hz}$, 1 H), 7.03 (t, $J = 6.0\text{ Hz}$, 1 H), 7.16 (t, $J = 6.9\text{ Hz}$, 1 H), 7.27-7.38 (m, 6 H);

MS m/e 226 (MH^+);

25 Anal. Calcd for $\text{C}_{14}\text{H}_{11}\text{NO}_2$: C, 74.65; H, 4.92; N, 6.22

Found: C, 74.25; H, 4.99; N, 5.85.

86

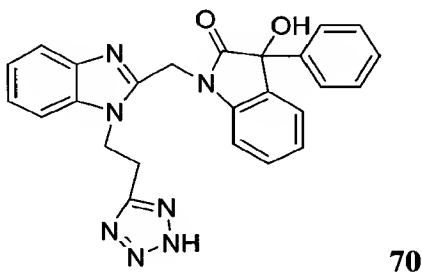


A mixture of compound **69c** (371 mg, 1.65 mmol), BTTP (609 mg, 1.95 mmol), and chloride **69b** (330 mg, 1.50 mmol) were stirred together in THF (10 mL) at room temperature for 1 hour. The solvent was evaporated and the residue was diluted with water and extracted with EtOAc. The combined organic extracts were washed with water, dried over MgSO₄, and evaporated. Purification by flash column chromatography (gradient, EtOAc/hexanes = 2:1 to EtOAc/MeOH = 10:1) gave 540 mg (88% yield) of compound **69** as a white solid:

¹H NMR (CDCl₃) δ 2.62-2.90 (m, 2 H), 4.50-4.80 (m, 2 H), 5.12 (d, J = 16.0 Hz, 1 H), 5.47 (bd, J = 16.0 Hz, 1 H), 7.05-7.80 (m, 13 H);

IR (KBr, cm⁻¹) 3409, 2252, 1720, 1613, 1467, 1361, 1170, 746;

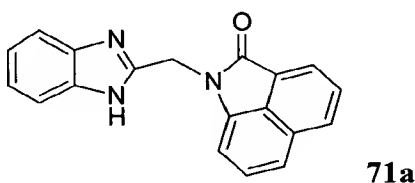
MS m/e 409 (MH⁺).



A mixture of compound **69** (450 mg, 1.10 mmol), sodium azide (215 mg, 3.50 mmol) and ammonium chloride (176 mg, 3.30 mmol) were stirred in DMF (15 mL) at 115 °C for 40 hours. The solvent was evaporated and the residue was diluted with 1 N NaOH and washed with Et₂O. The aqueous layer was then acidified with concentrated HCl and the solid collected by filtration. The solid was dissolved in a mixture of Et₂O and THF, dried over MgSO₄, and evaporated. The resulting residue was triturated in Et₂O and filtered. The solid was then

treated with 1 equivalent of 1 N NaOH in MeOH. The solvent was evaporated and the residue was triturated in Et₂O to give 258 mg (50% yield) of compound **70** as sodium salt:

- 5 ¹H NMR (DMSO-d₆) δ 2.83-2.88 (m, 1 H), 3.10-3.15 (m, 1 H), 4.46-4.56 (m, 2 H), 5.04 (d, J = 16.5 Hz, 1 H), 5.18 (d, J = 16.5 Hz, 1 H), 6.93 (d, J = 8.0 Hz, 1 H), 6.98 (d, J = 7.3 Hz, 1 H), 7.11 (d, J = 7.5 Hz, 1 H), 7.15-7.21 (m, 6 H), 7.48 (d, J = 7.9 Hz, 2 H), 7.54 (d, J = 8.9 Hz, 2 H);
IR (KBr, cm⁻¹) 3202, 1716, 1613, 1487, 1467, 1424, 1365, 1171, 745;
10 MS m/e 452 (MH⁺).



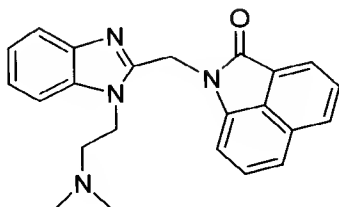
- A mixture of benz[c,d]indol-2(1*H*)-one (2.00 g, 11.82 mmol) and NaH
15 (60% suspension in mineral oil, 567 mg, 14.19 mmol) in CH₃CN (30 mL) was stirred at room temperature for 30 minutes. Compound **1b** (4.77 g, 14.19 mmol) was added and the reaction was stirred at 60°C for 72 hours. The reaction was quenched with saturated aqueous NaHCO₃ and extracted with CH₂Cl₂. The organic extracts were dried over MgSO₄ and evaporated to give 5.00 g of a crude
20 mesyl protected product. The crude material was treated with excess hydrazine hydrate (20.42 g, 0.64 mol) in a mixture of MeOH and CH₂Cl₂, and the mixture was stirred at reflux for 18 hours. The solvent was evaporated and the residue was diluted with water and extracted with EtOAc. The extracts were dried over MgSO₄ and concentrated. Purification by flash column chromatography
25 (gradient, CH₂Cl₂/EtOAc, 4:1 to 1:4) gave 2 g (57% yield) of compound **71a**:

¹H NMR (CDCl₃) δ 5.39 (s, 2 H), 7.19-7.25 (m, 3 H), 7.42-7.64 (m, 5 H), 7.95-8.00 (m, 2 H);
IR (KBr, cm⁻¹) 3227, 1686, 1625, 1492, 1318, 776, 737;

MS m/e 300 (MH⁺);

Anal. Calcd for C₁₉H₁₃N₃O • 0.2 H₂O: C, 75.33; H, 4.46; N, 13.87

Found: C, 75.57; H, 4.26; N, 13.81.

**71**

Compound **71a** (600 mg, 2.00 mmol) and NaH (60 % suspension in mineral oil, 240 mg, 6.00 mmol) in a mixture of toluene and DMF (30 mL, 3:1) were stirred at room temperature for 30 minutes. 2-Chloro-N,N-dimethylethylamine hydrochloride (317 mg, 2.20 mmol) was added and the reaction mixture was stirred at 55 °C for 18 hours. The reaction was diluted with saturated aqueous NaHCO₃ and extracted with Et₂O. The organic extracts were dried over MgSO₄ and evaporated. Purification by flash column chromatography (EtOAc/acetone, 3.5:1) gave 248 mg (33% yield) of compound **71**. Treatment of the free amine in MeOH with excess 4N HCl in dioxane followed by evaporation of the solvent gave the HCl salt of compound **71**:

¹H NMR (CD₃OD) δ 3.14 (s, 6 H), 3.84-3.89 (m, 2 H), 5.16-5.22 (m, 2 H), 5.92 (s, 2 H), 7.43 (d, J = 7.1 Hz, 1 H), 7.60-7.74 (m, 4 H), 7.88-7.93 (m, 2 H), 8.09 (d, J = 8.1 Hz, 1 H), 8.20 (d, J = 6.9 Hz, 1 H), 8.27 (d, J = 8.1 Hz, 1 H);

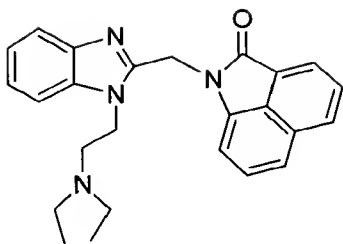
IR (KBr, cm⁻¹) 3391, 1706, 1633, 1470, 1305, 964, 828, 756;

MS m/e 371 (MH⁺);

Anal. Calcd for C₂₃H₂₂N₄O • 2 HCl • 3 H₂O: C, 55.54; H, 6.08; N, 11.26

Found: C, 55.73; H, 6.14; N, 11.03.

89



72

Compound **72** was prepared using the same procedure as compound **71** with 2-(diethylamino)ethyl chloride hydrochloride in 63% yield:

5

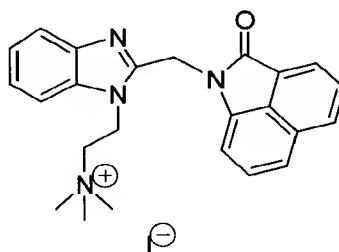
^1H NMR (CD_3OD) δ 1.45 (t, $J = 7.3$ Hz, 6 H), 3.46-3.51 (m, 4 H), 3.82 (t, $J = 8.1$ Hz, 2 H), 5.23 (t, $J = 8.0$ Hz, 2 H), 5.91 (s, 2 H), 7.42 (d, $J = 7.1$ Hz, 1 H), 7.59-7.78 (m, 5 H), 7.86-7.92 (m, 1 H), 8.10 (d, $J = 8.2$ Hz, 1 H), 8.19 (d, $J = 7.0$ Hz, 1 H), 8.26 (d, $J = 8.2$ Hz, 1 H);

10 IR (KBr, cm^{-1}) 3445, 2947, 1717, 1633, 1473, 1394, 1303, 966, 830, 781, 749;

MS m/e 399 (MH^+);

Anal. Calcd for $\text{C}_{25}\text{H}_{26}\text{N}_4\text{O} \cdot 2 \text{HCl} \cdot 3 \text{H}_2\text{O}$: C, 57.14; H, 6.52; N, 10.66

Found: C, 56.96; H, 6.48; N, 10.40.



73

15

To a solution of amine **71** (50 mg, 0.14 mmol) in acetone (1.5 mL) was added methyl iodide (19 mg, 0.14 mmol). The reaction mixture was stirred under N_2 atmosphere at ambient temperature for 16 hours. The precipitate was filtered, washed with ether and dried to give 17 mg (24% yield) of compound **73**:

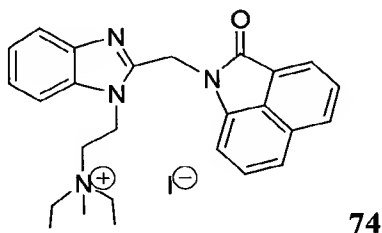
20

^1H NMR (CD_3OD) δ 3.43 (s, 9 H), 3.85-3.90 (m, 2 H), 5.00-5.05 (m, 2 H), 5.56 (s, 2 H), 7.33-7.42 (m, 3 H), 7.51-7.56 (m, 1 H), 7.63-7.71 (m, 3 H), 7.81-7.86 (m, 1 H), 8.14-8.20 (m, 2 H);

MS m/e 385 (MH^+).

5 Anal. Calcd for $\text{C}_{24}\text{H}_{25}\text{IN}_4\text{O} \cdot 0.50 \text{ H}_2\text{O}$: C, 55.29; H, 5.03; N, 10.75

Found: C, 55.10; H, 5.01; N, 10.59.



10 Compound **74** was prepared using the same procedure as compound **73** with compound **72** and methyl iodide in 49% yield:

^1H NMR (CDCl_3) δ 1.44 (t, $J = 7.2$ Hz, 6 H), 3.31 (s, 3 H), 3.64 (q, $J = 7.2$ Hz, 4 H), 3.75-3.81 (m, 2 H), 4.97-5.03 (m, 2 H), 5.56 (s, 2 H), 7.31-7.43 (m, 3 H),

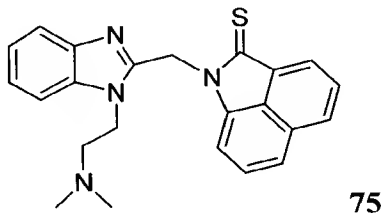
15 7.51-7.72 (m, 4 H), 7.81-7.86 (m, 1 H), 8.14-8.20 (m, 2 H);

IR (KBr, cm^{-1}) 3011, 1693, 1634, 1493, 1460, 1427, 1092, 774, 747;

MS m/e 413 (MH^+);

Anal. Calcd for $\text{C}_{26}\text{H}_{29}\text{IN}_4\text{O}$: C, 57.79; H, 5.41; N, 10.37

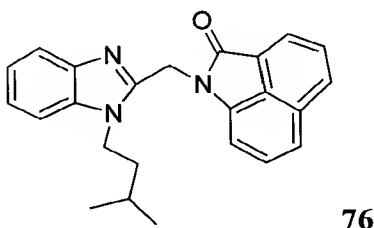
Found: C, 57.67; H, 5.38; N, 10.37.



20 To a solution of compound **71** (74 mg, 0.20 mmol) in toluene (7 mL) was added 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide

(Lawesson's reagent, 51 mg, 0.13 mmol). The reaction mixture was stirred at reflux for 4 hours. The solvent was evaporated and the residue was subjected to column chromatography (gradient, straight EtOAc to EtOAc/acetone, 2:1). The product was triturated with ether and then dried *in vacuo* to give 65 mg (77% yield) of compound **75**:

^1H NMR (DMSO- d_6) δ 2.20 (s, 6 H), 2.58-2.64 (m, 2 H), 4.48-4.52 (m, 2 H), 5.97 (s, 2 H), 7.11-7.16 (m, 1 H), 7.19-7.25 (m, 1 H), 7.40 (d, $J = 7.2$ Hz, 1 H), 7.46 (d, $J = 7.9$ Hz, 1 H), 7.55-7.62 (m, 2 H), 7.83 (d, $J = 8.3$ Hz, 1 H), 7.89 (d, $J = 7.9$ Hz, 1 H), 8.23 (d, $J = 7.1$ Hz, 1 H), 8.32 (d, $J = 8.1$ Hz, 1 H);
IR (KBr, cm^{-1}) 3436, 1493, 1471, 1373, 1313, 1280, 1231, 970, 818, 767, 745;
MS m/e 387 (MH^+).



15

Compound **76** was prepared using the same procedure as compound **71** with 1-bromo-3-methylbutane in 35% yield:

^1H NMR (CD_3OD) δ 0.92 (d, $J = 6.2$ Hz, 6 H), 1.65-1.69 (m, 3 H); 4.56-4.62 (m, 2 H), 5.79 (s, 2 H), 7.24 (d, $J = 7.2$ Hz, 1 H), 7.56-7.67 (m, 2 H), 7.71-7.77 (m, 2 H), 7.86-7.89 (m, 1 H), 7.91 (d, $J = 7.1$ Hz, 1 H), 8.19 (d, $J = 7.0$ Hz, 1 H), 8.26 (d, $J = 8.1$ Hz, 1 H);

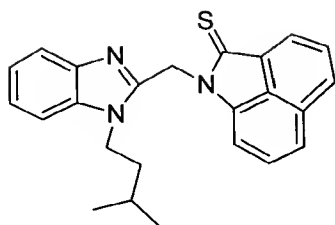
IR (KBr, cm^{-1}) 3449, 2453, 1709, 1493, 1470, 1293, 831, 781, 750;

MS m/e 370 (MH^+);

25 Anal. Calcd for $\text{C}_{24}\text{H}_{23}\text{N}_3\text{O} \cdot \text{HCl} \cdot 1.5\text{H}_2\text{O}$: C, 66.58; H, 6.29; N, 9.71

Found: C, 66.68; H, 6.20; N, 9.53.

92



77

Compound **77** was prepared using the same procedure as compound **75** with compound **76**:

5

^1H NMR (CD_3OD) δ 0.71 (d, $J = 6.6$ Hz, 6 H), 1.14-1.25 (m, 2 H), 1.50-1.57 (m, 1 H), 4.22-4.28 (m, 2 H), 6.05 (s, 2 H), 7.25-7.35 (m, 2 H), 7.38 (d, $J = 7.8$ Hz, 1 H), 7.47 (d, $J = 7.2$ Hz, 1 H), 7.47 (d, $J = 7.2$ Hz, 1 H), 7.59 (d, $J = 8.3$ Hz, 1 H), 7.72 (d, $J = 7.6$ Hz, 1 H), 7.83-7.86 (m, 1 H), 8.05 (d, $J = 8.1$ Hz, 1 H), 8.28 (d, $J = 7.1$ Hz, 1 H);

10

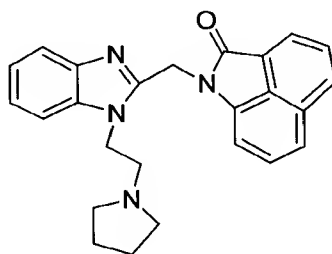
IR (KBr, cm^{-1}) 3441, 2959, 1610, 1493, 1471, 1372, 1281, 1231, 1208, 969, 819, 744;

MS m/e 386 (MH^+);

Anal. Calcd for $\text{C}_{24}\text{H}_{23}\text{N}_3\text{S} \cdot 0.4\text{H}_2\text{O}$: C, 73.40; H, 6.11; N, 10.70

15

Found: C, 73.60; H, 5.83; N, 10.53.



78

Compound **78** was prepared using the same procedure as compound **71** with 1-(2-chloroethyl)pyrrolidine hydrochloride in 46% yield:

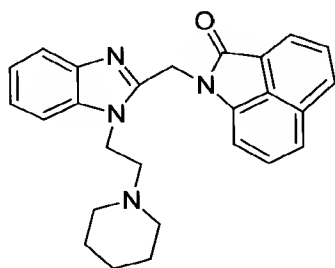
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^1H NMR (CDCl_3) δ 2.26 (bs, 4 H), 3.15-3.30 (m, 2 H), 3.70-3.90 (m, 4 H), 5.39 (bs, 2 H), 6.01 (s, 2 H), 7.41 (t, $J = 7.8$ Hz, 1 H), 7.50-7.60 (m, 3 H), 7.69-7.79 (m, 2 H), 8.03-8.12 (m, 3 H), 8.35 (d, $J = 8.3$ Hz, 1 H);
 IR (KBr, cm^{-1}) 3445, 2649, 1719, 1635, 1495, 1475, 1307, 969, 783, 747;

5 MS m/e 397 (MH^+);

Anal. Calcd for $\text{C}_{25}\text{H}_{24}\text{N}_4\text{O} \cdot 2\text{HCl} \cdot 1.5 \text{H}_2\text{O}$: C, 60.48; H, 5.89; N, 11.28

Found: C, 60.37; H, 5.98; N, 11.19



79

10

Compound **79** was prepared using the same procedure as compound **71** with 1-(2-chloroethyl)piperidine monohydrochloride in 60% yield:

^1H NMR (CDCl_3) δ 1.07-1.37 (m, 6 H), 2.20 (bs, 4 H), 2.31 (bs, 2 H), 4.26 (bs, 2 H), 5.35 (s, 2 H), 7.09-7.33 (m, 5 H), 7.36 (dd, $J = 1.2, 7.7$ Hz, 1 H), 7.57 (t, $J = 7.6$ Hz, 1 H), 7.61-7.67 (m, 1 H), 7.87 (d, $J = 8.1$ Hz, 1 H), 7.95 (d, $J = 7.0$ Hz, 1 H);

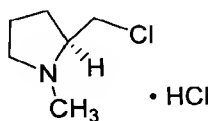
15

IR (KBr, cm^{-1}) 2920, 1707, 1476, 1397, 1309, 1093, 782, 748;

MS m/e 411 (MH^+);

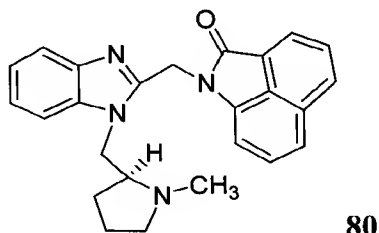
20 Anal. Calcd for $\text{C}_{26}\text{H}_{26}\text{N}_4\text{O} \cdot 0.3 \text{H}_2\text{O}$: C, 75.08; H, 6.45; N, 13.47

Found: C, 75.09; H, 6.45; N, 13.45.



80a

(S)-2-(chloromethyl)-1-methylpyrrolidine hydrochloride was prepared according to the procedure reported by S. D. Kimball et al. (*J. Med. Chem.* **1992**, *35*, 780-793).



5

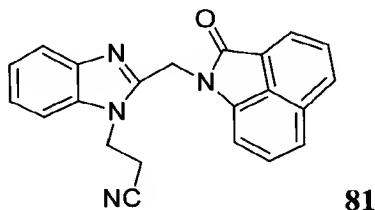
Compound **80** was prepared using the same procedure as compound **71** with compound **80a**:

¹H NMR (CD₃OD) δ 2.10-2.40 (m, 4 H), 3.13 (s, 3 H), 3.57-3.73 (m, 1 H), 3.85-3.95 (m, 1 H), 4.20-4.36 (m, 1H), 5.14 (dd, J = 8.9, 15.0 Hz, 1 H), 5.36 (dd, J = 5.7, 15.0 Hz, 1 H), 5.95 (s, 2 H), 7.39 (d, J = 7.1 Hz, 1 H), 7.62-7.79 (m, 5 H), 7.87-7.92 (m, 1 H), 8.10 (d, J = 9.0 Hz, 1 H), 8.19 (d, J = 6.9 Hz, 1 H), 8.26 (d, J = 8.1 Hz, 1 H);

MS m/e 397 (MH⁺);

Anal. Calcd for C₂₅H₂₄N₄ O•2HCl•2H₂O: C, 59.41; H, 5.98; N, 11.08

Found: C, 59.56; H, 5.75; N, 10.90.



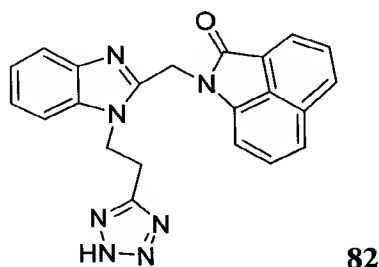
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A mixture of compound **71a** (1.00 g, 3.34 mmol), acrylonitrile (533 mg, 10.06 mmol), and 1,3,4,6,7,8-hexahydro-1-methyl-2H-pyrimido[1,2-a]pyrimidine (MTBD, 29 mg, 0.19 mmol) in CH₃CN (35 mL) was stirred at reflux for 18 hours. The solvent was evaporated and the residue was diluted with water

and extracted with EtOAc. The organic material was dried over MgSO₄ and evaporated. The resulting residue was triturated with Et₂O and filtered to give 1.0 g (85% yield) of compound **81** as a yellow solid:

- 5 ¹H NMR (CDCl₃) δ 2.72 (t, J = 6.8 Hz, 2 H), 4.75 (t, J = 6.8 Hz, 2 H), 5.50 (s, 2 H), 7.30-7.39 (m, 3 H), 7.44-7.50 (m, 2 H), 7.54-7.60 (m, 1 H), 7.75 (t, J = 8.0 Hz, 1 H), 7.81-7.85 (m, 1 H), 8.07 (d, J = 8.1 Hz, 1 H), 8.14 (d, J = 7.0 Hz, 1 H); IR (KBr, cm⁻¹) 3363, 2247, 1686, 1633, 1466, 1395, 1363, 1095, 772, 743; MS m/e 352 (MH⁺).

10

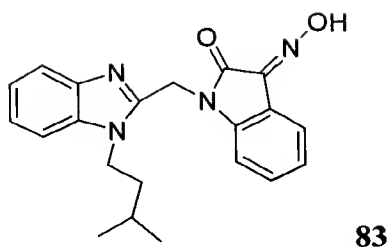


- 15 A mixture of compound **81** (980 mg, 2.78 mmol), sodium azide (542 mg, 8.34 mmol), and ammonium chloride (446 mg, 8.34 mmol) in DMF (20 mL) was stirred at 95 °C for 72 hours. The solvent was evaporated under reduced pressure. The residue was dissolved in water and washed with EtOAc. The pH of the aqueous layer was adjusted to 7 and the yellow precipitate was collected to give 1.2 g (quantitative yield) of compound **82**:

- 20 ¹H NMR (CDCl₃) δ 3.41 (t, J = 6.9 Hz, 2 H), 4.83 (t, J = 6.9 Hz, 2 H), 5.25 (s, 2 H), 6.84 (d, J = 6.2 Hz, 1 H), 6.98 (d, J = 7.1 Hz, 1 H), 7.18-7.56 (m, 3 H), 7.64 (d, J = 8.5 Hz, 1 H), 7.71 (d, J = 8.1 Hz, 1 H), 7.82 (t, J = 8.0 Hz, 1 H), 8.11 (d, J = 7.0 Hz, 1 H), 8.16 (d, J = 8.1 Hz, 1 H); IR (KBr, cm⁻¹) 3343, 1693, 1577, 1472, 1397, 775, 742; MS m/e 396 (MH⁺);

Anal. Calcd for C₂₂H₁₆N₇O • 2.7 H₂O: C, 56.70; H, 4.63; N, 21.04

Found: C, 56.76; H, 4.53; N, 20.88.



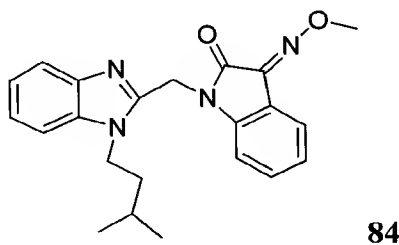
A mixture of isatin **54** (100 mg, 0.29 mmol) and hydroxylamine hydrochloride (200 mg 2.87 mmol) in MeOH (5 mL) was stirred at reflux for 1.5 hours. The solvent was evaporated and the residue was suspended in CH₂Cl₂. The filtrate was evaporated. The residue was purified by flash column chromatography (gradient, EtOAc:hexanes = 1:2 to 1:1) and the purified material was triturated with Et₂O/hexanes to give 13 mg (12% yield) of compound **83**:

¹H NMR (CD₃OD) δ 0.94 (d, J = 6.6 Hz, 6 H), 1.42-1.50 (m, 2 H), 1.65-1.74 (m, 1 H), 4.28-4.34 (m, 2 H), 5.32 (s, 2 H), 7.07-7.12 (m, 2 H), 7.23-7.35 (m, 3 H), 7.45 (d, J = 6.8 Hz, 1 H), 7.62 (d, J = 7.3 Hz, 1 H), 8.10 (d, J = 8.0 Hz, 1 H); IR (KBr, cm⁻¹) 2966, 1726, 1608, 1461, 1347, 1180, 1084, 1015, 738;

MS m/e 363 (MH⁺);

Anal. Calcd for C₂₁H₂₂N₄O₂: C, 69.59; H, 6.12; N, 15.46

Found: C, 69.22, H, 6.29; N, 15.20.



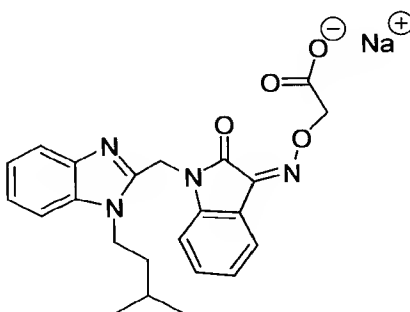
Compound **84** was prepared using the same procedure as compound **83** with *O*-methylhydroxylamine hydrochloride in 88% yield:

^1H NMR (CD_3OD) δ 0.96 (d, J = 6.6 Hz, 6 H), 1.45-1.53 (m, 2 H), 1.66-1.73 (m, 1 H), 4.30 (t over bs, 5 H), 5.30 (s, 2 H), 7.10 (d, J = 7.8 Hz, 2 H), 7.22-7.38 (m, 3 H), 7.46 (d, J = 8.4 Hz, 1 H), 7.61 (d, J = 7.2 Hz, 1 H), 7.97 (d, J = 7.5 Hz, 1 H); IR (KBr, cm^{-1}) 3431, 2952, 1724, 1608, 1468, 1353, 1010, 752;

5 MS m/e 377 (MH^+);

Anal. Calcd for $\text{C}_{22}\text{H}_{24}\text{N}_4\text{O}_2$: C, 70.19; H, 6.43; N, 14.88

Found: C, 69.89; H, 6.34; N, 14.80.

**85**

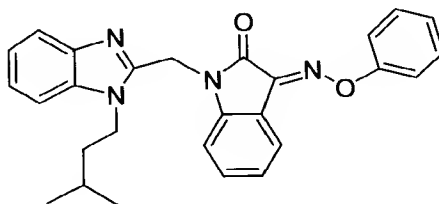
10

Compound **85** was prepared using the same procedure as compound **83** with carboxymethoxylamine hemihydrochloride. The sodium salt was prepared by adding 1 equivalent of 1N NaOH to the acid and evaporating the solvent:

15 ^1H NMR ($\text{DMSO}-d_6$) δ 0.82 (d, J = 6.7 Hz, 6 H), 1.31-1.41 (m, 2 H), 1.50-1.63 (m, 1 H), 3.95-4.05 (m, 2 H), 4.83 (s, 2 H), 4.93 (s, 2 H), 6.74-6.86 (m, 1 H), 7.00-7.03 (m, 2 H), 7.03-7.05 (m, 1 H), 7.15 (bs, 2 H), 7.63-7.65 (m, 1 H), 7.84-7.89 (m, 1 H);

MS m/e 421 (MH^+).

20

**86**

Compound **86** was prepared using the same procedure as compound **83** with *O*-phenylhydroxylamine hydrochloride:

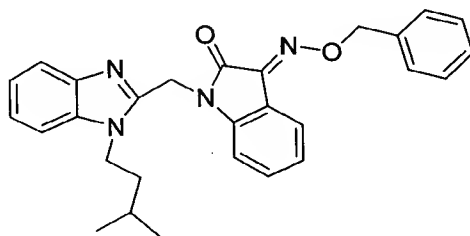
¹H NMR (CD₃OD) δ 0.91 (d, J = 6.5 Hz, 6 H), 1.44-1.49 (m, 2 H), 1.65-1.69 (m, 1 H), 4.30 (t, J = 8.3 Hz, 5 H), 5.32 (s, 2 H), 5.52 (s, 2 H), 7.07-7.09 (m, 2 H), 7.24-7.41 (m, 6 H), 7.45-7.50 (m, 3 H), 7.61 (d, J = 7.4 Hz, 1 H), 7.96 (d, J = 7.6 Hz, 1 H);

IR (KBr, cm⁻¹) 3443, 2951, 1731, 1607, 1467, 1372, 1332, 979, 744;

MS m/e 453 (MH⁺);

10 Anal. Calcd for C₂₂H₂₄N₄O₂ : C, 74.31; H, 6.24; N, 12.38

Found: C, 74.02; H, 6.14; N, 12.36.

**87**

15 Compound **87** was prepared using the same procedure as compound **83** with *O*-benzylhydroxylamine hydrochloride in 78% yield:

¹H NMR (CD₃OD) δ 0.91 (d, J = 6.5 Hz, 6 H), 1.44-1.49 (m, 2 H), 1.65-1.69 (m, 1 H), 4.30 (t, J = 8.3 Hz, 5 H), 5.32 (s, 2 H), 5.52 (s, 2 H), 7.07-7.09 (m, 2 H), 7.24-7.41 (m, 6 H), 7.45-7.50 (m, 3 H), 7.61 (d, J = 7.4 Hz, 1 H), 7.96 (d, J = 7.6 Hz, 1 H);

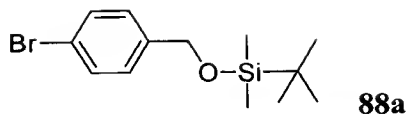
IR (KBr, cm⁻¹) 3443, 2951, 1731, 1607, 1467, 1372, 1332, 979, 744;

MS m/e 453 (MH⁺);

Anal. Calcd for C₂₂H₂₄N₄O₂ : C, 74.31; H, 6.24; N, 12.38

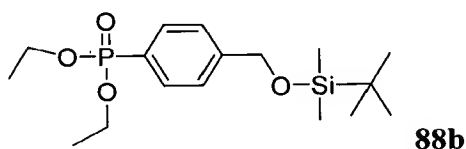
25 Found: C, 74.02; H, 6.14; N, 12.36.

99

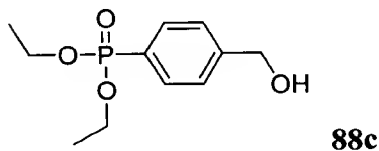


To a solution of 4-bromobenzyl alcohol (56.8 g, 0.304 mol) and imidazole (31.0 g, 0.456 mol) in THF (500 ml) at 0 °C was added TBDMS chloride (50.3 g, 0.334 mol) in one portion. After stirring at room temperature for 1 hour, the suspension was filtered. The filtrate was diluted with EtOAc (500 ml), washed with water and brine, dried over MgSO₄, and concentrated. The residue was distilled under vacuum to provide 84.6 g (92% yield) of compound **88a** as a colorless oil:

¹H NMR (CDCl₃) δ 0.95 (s, 9 H), 4.69 (s, 2 H), 7.21 (d, J = 7.5 Hz, 2 H), 7.44 (d, J = 7.5 Hz, 2 H);
MS m/e 282 (MH⁺).

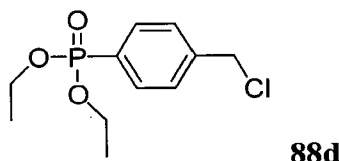


To a solution of bromide **88a** (73.0 g, 0.242 mol) in THF (500 ml) at -78 °C was added *t*-BuLi (1.7 M in heptane, 314 ml, 0.533 mol) dropwise. The mixture was stirred at -78 °C for 30 minutes before addition of diethyl chlorophosphate (43.9 g, 0.254 mol). The reaction mixture was stirred for 2 hours and was quenched with saturated NH₄Cl. The organic layer was washed with brine, dried over MgSO₄, and concentrated. The crude product **88b** was used for the next reaction without further purification.



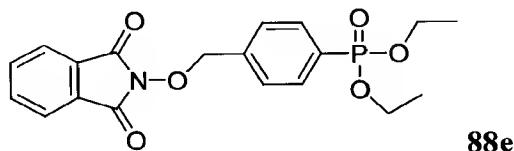
To a solution of compound **88b** (31.1 g, 86.8 mmol) in THF (300 ml) at 0 °C was added TBAF (1M in THF, 104 ml, 104 mmol). The reaction mixture was stirred for 2 hours and was quenched with saturated NH_4Cl . The organic layer was diluted with EtOAc (300 ml), washed with water and brine, dried over MgSO_4 , and concentrated. The crude alcohol product **88c** was used for the next reaction without further purification:

^1H NMR (CDCl_3) δ 1.28 (t, J = 7.2 Hz, 6 H), 4.00-4.11 (m, 4 H), 4.71 (s, 2 H), 7.42 (dd, J = 3.6, 8.0 Hz, 2 H), 7.70 (dd, J = 8.0, 12.9 Hz, 2 H).



Chloride **88d** was prepared using the same procedure as compound **4c** with compound **88c** and thionyl chloride:

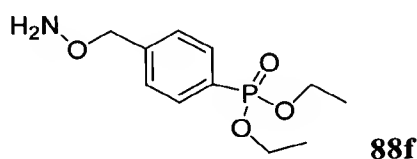
^1H NMR (CDCl_3) δ 1.31 (t, J = 7.2 Hz, 6 H), 4.05-4.16 (m, 4 H), 4.59 (s, 2 H), 7.48 (dd, J = 3.9, 8.0 Hz, 2 H), 7.80 (dd, J = 8.0, 13.2 Hz, 2 H); MS m/e 262 (MH^+).



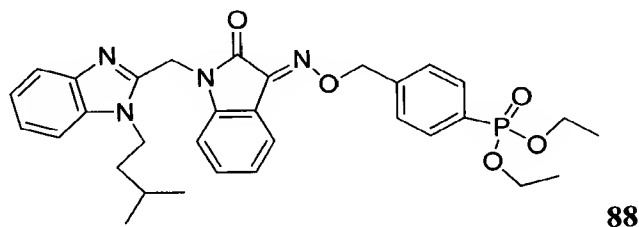
A mixture of N-hydroxyphthalimide (0.90 g, 5.5 mmol), compound **88d** (1.32 g, 5.0 mmol), and DIEA (1.26 g, 10 mmol) in CH_3CN (50 ml) was stirred at reflux for 4 hours. The resulting solution was diluted with CH_2Cl_2 (100 mL) and washed with saturated NaHCO_3 . The organic layer was dried over MgSO_4 and concentrated. The residue was purified by flash chromatography (gradient,

CH₂Cl₂:MeOH = 40:1 to 30:1) to give 1.39 g (65% yield) of compound **88e** as a viscous oil:

¹H NMR (CD₃OD) δ 1.28-1.33 (m, 6 H), 4.08-4.13 (m, 4 H), 5.25 (s, 2 H), 7.47-7.50 (m, 2 H), 7.77-7.82 (m, 8 H);
MS m/e 390 (MH⁺).



10 A solution of compound **88e** (1.50 g, 3.85 mmol) and hydrazine (0.33 g, 9.6 mmol) in MeOH (50 ml) was stirred at reflux for 12 hours. The mixture was filtered and the filtrate was concentrated. Trituration of the residue with hot CHCl₃ (50 ml), followed by filtration and concentration of the filtrate gave 0.90 g (90% yield) of compound **88f** as a viscous oil, which was used without further
15 purification.



A mixture of compound **54** (902 mg, 2.60 mmol), compound **88f** (808 mg, 3.12 mmol) and *p*-toluenesulphonic acid (99 mg, 0.52 mmol) in MeOH (26 ml) was stirred at reflux for 1 hour. The reaction mixture was diluted with CH₂Cl₂ (100 ml), washed with saturated NaHCO₃, dried over MgSO₄, and concentrated. The residue was purified by flash chromatography (gradient, CH₂Cl₂:MeOH = 40:1 to 20:1) to give 1.29 g (84% yield) of compound **88** as a yellow foam:

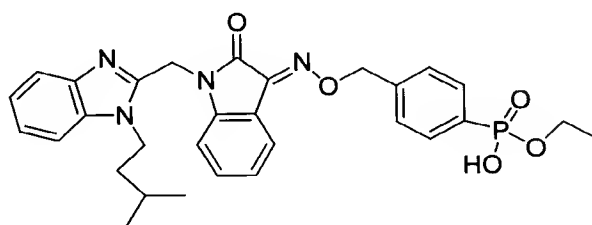
^1H NMR (CD_3OD) δ 0.91 (d, J = 6.6 Hz, 6 H), 1.34 (t, J = 7.2 Hz, 6 H), 1.46-1.54 (m, 2 H), 1.64-1.71 (m, 1 H), 4.07-4.30 (m, 4 H), 4.32 (t, J = 8.2 Hz, 2 H), 5.33 (s, 2 H), 5.62 (s, 2 H), 7.09-7.16 (m, 2 H), 7.26-7.37 (m, 2 H), 7.39-7.42 (m, 1 H), 7.48-7.50 (m, 1 H), 7.62-7.70 (m, 3 H), 7.79-7.84 (m, 2 H), 8.04-8.07 (m, 1 H);

5 IR (KBr, cm^{-1}) 3436, 2957, 1727, 1607, 1468, 1023;

MS m/e 588 (MH^+);

Anal. Calcd for $\text{C}_{32}\text{H}_{37}\text{N}_4\text{O}_5\text{P}\cdot\text{H}_2\text{O}$: C, 63.36; H, 6.48; N, 9.24

Found: C, 63.34; H, 6.48; N, 9.15.



89

10

Compound **88** (294 mg, 0.5 mmol) and 1 N NaOH (1.50 ml, 1.50 mmol) in a mixture of MeOH and H_2O (20 ml, 1:1) was heated to reflux for 12 hours. The mixture was acidified with 1 N HCl to pH 2 and concentrated. The residue
 15 was purified by prep-HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) to give 360 mg (56% yield) of compound **89** as a yellow gel:

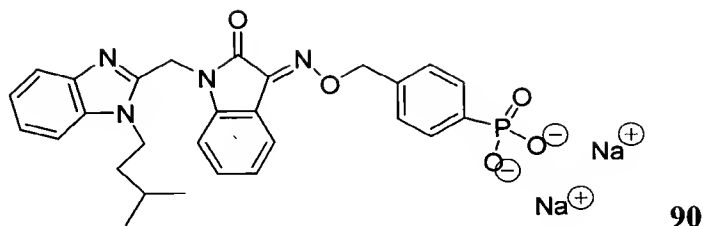
^1H NMR (CD_3OD) δ 0.94 (d, J = 6.6 Hz, 6 H), 1.19 (t, J = 7.1 Hz, 3 H), 1.46-1.53 (m, 2 H), 1.66-1.75 (m, 1 H), 3.76-3.86 (m, 2 H), 4.33 (t, J = 8.3 Hz, 2 H), 5.34 (s, 2 H), 5.57 (s, 2 H), 7.08-7.13 (m, 2 H), 7.25-7.40 (m, 3 H), 7.47-7.55 (m, 3 H), 7.64 (d, J = 7.3 Hz, 1 H), 7.80-7.87 (m, 2 H), 8.00-8.03 (m, 1 H);

IR (KBr, cm^{-1}) 3436, 2959, 1684, 1210, 1135;

MS m/e 561 (MH^+);

25 Anal. Calcd for $\text{C}_{30}\text{H}_{33}\text{N}_4\text{O}_5\text{P}\cdot 4\text{H}_2\text{O}\cdot 0.5\text{TFA}$: C, 52.32; H, 5.74; N, 7.87

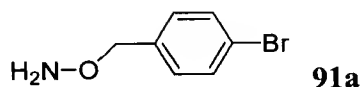
Found: C, 52.66; H, 5.66; N, 7.94.



To a solution of compound **88** (720 mg, 1.22 mmol) in CH₃CN (25 ml) at 0°C was added TMS bromide (1.86 g, 12.2 mmol) and stirred at room temperature for 12 hours. The mixture was concentrated and the residue was purified by preparative HPLC (gradient, 10% MeOH in H₂O with 0.1% TFA to 90% MeOH in H₂O with 0.1% TFA) to give 474 mg (73% yield) yellow powder. To a mixture of this yellow solid (60 mg, 0.11 mmol) in MeOH (2 ml) and H₂O (1 ml) was added 1N NaOH (0.225 ml, 0.22 mmol). The solution was concentrated and the residue was triturated with hot EtOAc to give 59 mg (90%) of compound **90** as yellow solid:

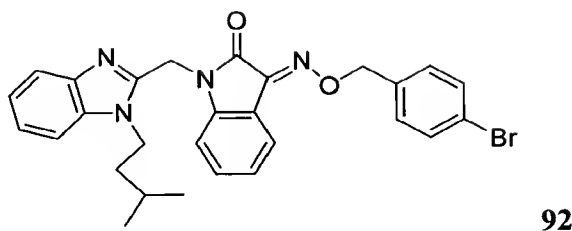
¹H NMR (CD₃OD) δ 0.98 (d, J = 6.6 Hz, 6 H), 1.48-1.55 (m, 2 H), 1.68-1.77 (m, 1 H), 4.34 (t, J = 8.2 Hz, 2 H), 5.34 (s, 2 H), 5.53 (s, 2 H), 7.04-7.14 (m, 2 H), 7.25-7.39 (m, 3 H), 7.42-7.50 (m, 3 H), 7.63-7.66 (m, 1 H), 7.90-7.96 (m, 3 H); IR (KBr, cm⁻¹) 3392, 2953, 1721, 1611, 1469, 970; MS m/e 533 (MH⁺);

Anal. Calcd for C₂₈H₂₇N₄Na₂O₅P•4H₂O•0.5TFA: C, 49.37; H, 5.07; N, 7.94
Found: C, 49.50; H, 5.47; N, 7.98.



Compound **91a** was prepared using the same procedure sequence as compound **88f** starting with 4-bromobenzyl bromide:

¹H NMR (DMSO-d₆) δ 6.09 (s, 2 H), 7.27-7.30 (m, 2 H), 7.52-7.55 (m, 2 H); MS m/e 203, 205 (MH⁺).



Compound **92** was prepared using the same procedure as compound **88**
5 with compound **91a**:

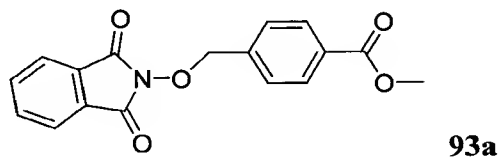
¹H NMR (DMSO-d₆) δ 0.92 (d, J = 6.6 Hz, 6 H), 1.55-1.59 (m, 2 H), 1.66-1.69
(m, 1 H), 4.38 (t, J = 7.7 Hz, 2 H), 5.42 (s, 2 H), 5.51 (s, 2 H), 7.13-7.20 (m, 2 H),
7.32-7.44 (m, 2 H), 7.45-7.47 (m, 3 H), 7.60-7.66 (m, 3 H), 7.70-7.71 (m, 1 H),
10 7.97 (d, J = 7.2 Hz, 1 H);

IR (KBr, cm⁻¹) 3445, 2956, 1727, 1607, 1468, 976;

MS m/e 531, 533 (MH⁺);

Anal. Calcd for C₂₈H₂₇BrN₄O₂: C, 63.28; H, 5.12; N, 10.54

Found: C, 63.03; H, 5.14; N, 10.48.



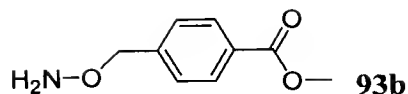
Compound **93a** was prepared using the same sequence of procedures as
compound **88e** starting with methyl 4-(bromomethyl)-benzoate:

20

¹H NMR (CDCl₃) δ 3.94 (s, 2 H), 5.29 (s, 2 H), 7.64 (d, J = 8.2 Hz, 2 H), 7.75-
7.85 (m, 4 H), 8.08 (d, J = 8.2 Hz, 2 H);

MS m/e 312 (MH⁺).

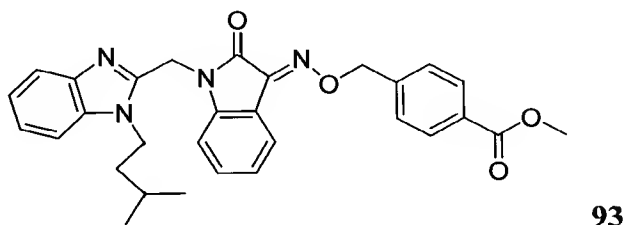
105



Compound **93b** was prepared using the same procedure as compound **88f** with compound **93a**:

5

^1H NMR (CDCl_3) δ 3.92 (s, 3 H), 4.75 (s, 2 H), 5.48 (bs, 2 H), 7.43 (d, $J = 8.3$ Hz, 2 H), 8.03 (d, $J = 8.3$ Hz, 2 H);
MS m/e 182 (MH^+).



10

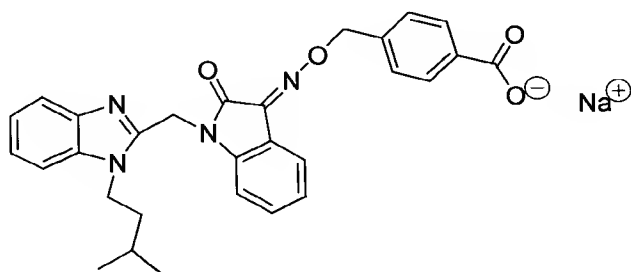
Compound **93** was prepared using the same procedure as compound **88** with compound **93b**:

15 ^1H NMR ($\text{DMSO}-d_6$) δ 0.89 (d, $J = 6.6$ Hz, 6 H), 1.40-1.70 (m, 3 H), 3.86 (s, 3 H), 4.25-4.30 (m, 2 H), 5.27 (s, 2 H), 5.62 (s, 2 H), 7.10-7.27 (m, 3 H), 7.43-7.62 (m, 6 H), 7.97-8.02 (m, 3 H);
MS m/e 511 (MH^+);

Anal. Calcd for $\text{C}_{30}\text{H}_{30}\text{N}_4\text{O}_4 \cdot 0.25\text{H}_2\text{O}$: C, 69.95; H, 5.97; N, 10.88

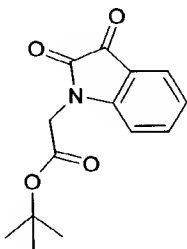
20

Found: C, 69.59; H, 5.68; N, 10.69.



Compound **93** (81 mg, 0.13 mmol) and 1N NaOH (0.39 mL, 0.39 mmol) were stirred at reflux in MeOH (5 mL). The solvent was evaporated and the residue was diluted with water. The aqueous material was adjusted to neutral pH with 1N HCl and extracted with EtOAc. The combined extracts were dried over
5 MgSO₄ and evaporated. The resulting acid was stirred with exactly 1 equivalent of 1N NaOH in MeOH and then the solvent was evaporated to give 24 mg (36% yield) of the sodium salt **94**:

¹H NMR (DMSO-d₆) δ 0.89 (d, J = 6.5 Hz, 6 H), 1.42-1.66 (m, 3 H), 4.26 (bt, J =
10 8.1 Hz, 2 H), 5.26 (s, 2 H), 5.60 (s, 2 H), 7.09-7.52 (m, 8 H), 7.58 (d, J = 8.1 Hz, 2 H), 7.98 (d, J = 8.1 Hz, 2 H);
MS m/e 497 (MH⁺).

**95a**

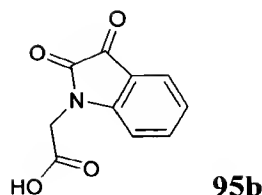
15

A solution of isatin (10 g, 68 mmol) and *t*-butyl bromoacetate (10 mL, 68 mmol) and K₂CO₃ (18.8 g, 136 mmol) in CH₃CN (50 mL) was heated to reflux for 3 hours then cooled, filtered and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc = 9:1) to give 8.38 g (47% yield) of
20 compound **95a** as an orange solid:

¹H NMR (DMSO-d₆) δ 1.41 (s, 9 H), 4.50 (s, 2 H), 7.17 (t, J = 8.4 Hz, 2 H), 7.60 (d, J = 8.5 Hz, 1 H), 7.68 (t, J = 8.4 Hz, 1 H);
MS m/e 261 (MH⁺);

25 Anal. Calcd for C₁₄H₁₅NO₄: C, 64.36; H, 5.79; N, 5.36
Found: C, 64.41; H, 5.96; N, 5.28.

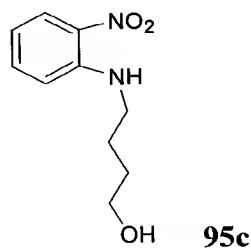
107



A mixture of ester **95a** (5.0 g, 19.10 mmol) and TFA (20 mL) was stirred at room temperature for 12 hours. The solvent was removed and the residue was dried under vacuum to give 3.5 g (77% yield) of compound **95b** as an orange solid:

¹H NMR (DMSO-d₆) δ 4.50 (s, 2 H), 7.15-7.20 (m, 2 H), 7.60 (d, J = 8.5 Hz, 1 H), 7.68 (t, J = 8.4 Hz, 1 H);

MS m/e 205 (MH⁺).



A solution of 2-fluoronitrobenzene (5.0 g, 35.50 mmol) and 1-amino-4-butanol (3.2 g, 35.50 mmol) in CH₃CN (100 mL) and triethylamine (4.0 g, 35.5 mmol) was heated to reflux for 12 hours, then cooled and concentrated. The residue was dissolved in EtOAc and washed with 1N HCl. The mixture was dried over MgSO₄ and concentrated to give 7.21 g (97% yield) of compound **95c** as a dark orange solid:

20

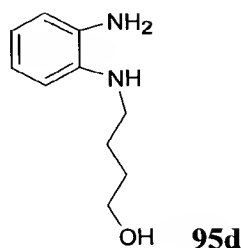
¹H NMR (DMSO-d₆) δ 1.45-1.56 (m, 2 H), 1.58-1.69 (2 H), 3.35 (t, J = 6.7 Hz, 2 H coupled to proton exchangeable in D₂O), 3.43 (t, J = 6.4 Hz, 2 H), 3.90-4.00 (br, 1 H, exchanges with D₂O), 6.66 (t, J = 6.0 Hz, 1 H), 7.04 (d, J = 9.0 Hz, 1 H),

7.52 (t, $J = 7.2$ Hz, 1 H), 8.04 (d, $J = 1.6, 7.2$ Hz, 1 H), 8.13 (bs, 1 H, exchanges with D_2O , 1 H);

IR (KBr cm^{-1}) 1350, 1154;

MS m/e 211 (MH^+);

- 5 Anal. Calcd for $C_{10}H_{14}N_2O_3 \cdot 0.28 H_2O$: C, 55.80; H, 6.82; N, 13.01
Found: C, 55.80; H, 6.62; N, 12.97.



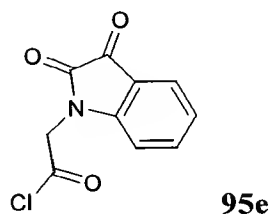
- 10 A solution of the nitro compound **95c** (5.0 g, 23.80 mmol) in ethanol (50 mL) was hydrogenated at 40 psi with 10% palladium on carbon (100 mg) for 4 hours. The catalyst was removed by filtration and the solvent was evaporated to give 4.3 g (99% yield) of compound **95d** as a dark oil:

- 15 1H NMR ($DMSO-d_6$) δ 1.47-1.66 (m, 4 H), 2.99 (t, $J = 6.6$ Hz, 2 H), 3.43 (t, $J = 6.6$ Hz, 2 H), 4.31-4.50 (br, exchange with D_2O , 4 H), 6.36-6.42 (m, 2 H) 6.54-6.82 (m, 2 H);

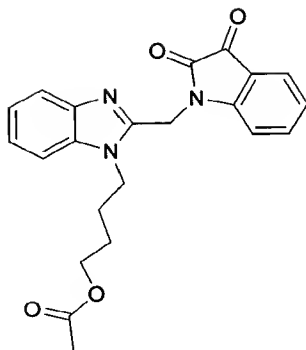
IR (film cm^{-1}) 1055, 739;

MS m/e 181 (MH^+);

- 20 Anal. Calcd for $C_{10}H_{16}N_2O \cdot 0.71 H_2O$: C, 62.23; H, 9.10; N, 14.51
Found: C, 62.23; H, 8.78; N, 14.41.

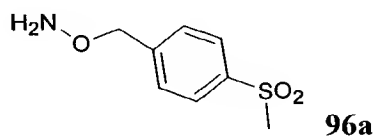


109

**95**

To a solution of compound **95d** (4.97 g, 27.60 mmol) and triethylamine (3.0 g, 30 mmol) in CH₂Cl₂ (100 mL) at -78°C was added compound **95e** (freshly prepared from compound **95b** (5.66g, 27.60 mmol) and oxalyl chloride (3.5 g, 27.60 mmol)) in CH₂Cl₂ (50 mL). The mixture was stirred at -78°C for 1 hour then warmed to room temperature and stirred for 12 hours. The solvent was removed. The residue was dissolved in AcOH (100 mL) and heated to reflux for 12 hours. The solvent was evaporated and the residue was purified by flash chromatography (hexanes:EtOAc = 3:1) to give 2.2 g (20% yield) of compound **95** as a yellow solid:

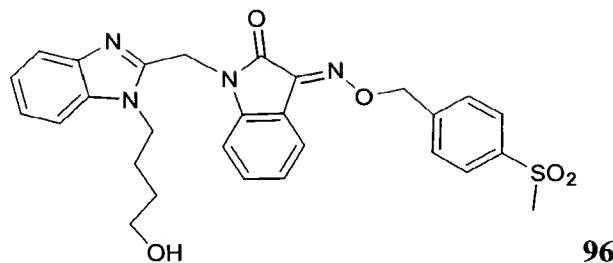
¹H NMR (DMSO-d₆) δ 1.63-1.66 (m, 2 H), 1.77-1.81 (m, 2 H), 1.90 (s, 3 H), 1.99 (s, 3 H), 4.03 (t, J = 6.6 Hz, 2 H), 4.34 (t, J = 7.5 Hz, 2 H), 5.24 (s, 2 H), 7.14-7.19 (m, 2 H), 7.25 (t, J = 8.2 Hz, 1 H), 7.31 (d, J = 8.0 Hz, 1 H), 7.58-7.67 (m, 4 H); MS m/e 391 (MH⁺).

**96a**

20

Compound **96a** was prepared using the same procedure sequence as compound **88f** starting with *p*-methylsulfonylbenzyl chloride.

110



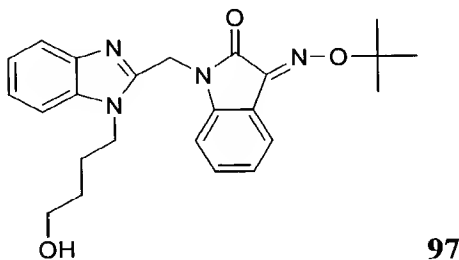
A mixture of compound **95** (0.39 g, 0.99 mmol) and **96a** (0.2 g, 0.99 mmol) in EtOH (50 mL) was heated to reflux for 12 hours. The solution was concentrated and filtered to give 195 mg (34% yield) of intermediate as a yellow solid. The solid was dissolved in MeOH (50 mL) and treated with *p*-toluenesulfonic acid (0.21 g, 1.10 mmol) and stirred at reflux for 12 hours. The mixture was cooled, concentrated. The residue was dissolved in EtOAc and washed with saturated aqueous NaHCO₃, dried over MgSO₄ and concentrated. The residue was dissolved in a minimum of MeOH and diluted with water. After standing for 1 hour, the precipitated product was isolated by filtration to give 0.12 g (66% yield) of compound **96** as a yellow solid:

¹H NMR (DMSO-*d*₆) δ 1.40-1.55 (m, 2 H), 1.70-1.80 (m, 2 H), 3.19 (s, 3 H), 3.38-3.99 (m, 2 H), 4.31-4.33 (m, 2 H), 5.26 (s, 2 H), 5.65 (s, 2 H), 7.11-7.24 (m, 4 H), 7.45 (t, *J* = 7.8 Hz, 1 H), 7.55 (t, *J* = 6.8 Hz, 2 H), 7.73 (d, *J* = 7.6 Hz, 2 H), 7.98 (d, *J* = 8.2 Hz, 2 H), 7.90-8.00 (m, 1 H);

MS *m/e* 532 (MH⁺);

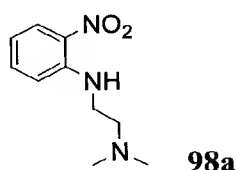
Anal. Calcd for C₂₈H₂₈N₄O₅•0.6 H₂O: C, 61.89; H, 5.42; N, 10.31

Found: C, 61.93; H, 5.23; N, 10.33.



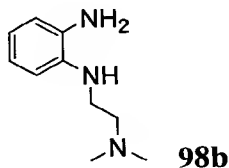
Compound **97** was prepared using the same procedure as compound **96** with *O*-(*tert*-butyl)hydroxylamine hydrochloride:

¹H NMR (DMSO-*d*₆) δ 1.15 (s, 9 H), 1.45-1.48 (m, 2 H), 1.75-1.80 (m, 2 H), 3.40 (t, *J* = 6.2 Hz, 2 H), 4.29 (t, *J* = 7.6 Hz, 2 H), 4.52 (d, *J* = 5.3 Hz, 2 H), 4.85-4.96 (bs, 1 H), 6.55-6.61 (m, 1 H), 6.84-6.87 (m, 1 H); 7.04-7.07 (m, 2 H), 7.17-7.21 (m, 2 H), 7.54 (d, *J* = 7.9 Hz, 1 H), 7.61 (d, *J* = 7.7 Hz, 1 H);
MS *m/e* 421 (MH⁺).



To a mixture of 2-fluoronitrobenzene (16.8 g, 119 mmol) and sodium acetate (300 mg) was added *N,N*-dimethylethylenediamine (12.5 mL, 113 mmol). After heating to 80 °C for 1 hour, the mixture was poured into water, and
15 extracted with EtOAc. The combined organic layers were dried over MgSO₄ and evaporated. The crude material was purified by silica gel chromatography (gradient, 1:1 EtOAc:Hexanes to 5% MeOH in EtOAc) to provide 12.0 g (50% yield) of compound **98a** as an orange oil:

20 ¹H NMR (CDCl₃) δ 2.30 (s, 6 H), 2.63 (t, *J* = 6.3 Hz, 2 H), 3.33-3.37 (m, 2 H), 6.63 (t, *J* = 8.3 Hz, 1 H), 6.82 (d, *J* = 8.3 Hz, 1 H), 7.43 (t, *J* = 8.1 Hz, 1 H), 8.17 (d, *J* = 8.5 Hz, 1 H), 8.33 (bs, 1 H);
MS *m/e* 209 (MH⁺).



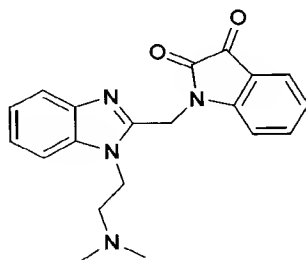
A mixture of compound **98a** (10.0 g, 47.7 mmol) and 10% palladium on carbon (500 mg) in EtOH (100 mL) was hydrogenated at 50 psi for 1 hour. The mixture was filtered through a pad of celite and the filtrate was evaporated. The residue was recrystallized from hexanes to give 7.52 g (88% yield) of compound

5 **98b** as flaky brown solid:

^1H NMR (CDCl_3) δ 2.26 (s, 6 H), 2.60 (t, $J = 6.1$ Hz, 2 H), 3.33-3.37 (t, $J = 6.1$ Hz, 2 H), 6.65-6.72 (m, 3H), 6.81 (t, $J = 7.5$ Hz, 1H);

MS m/e 179 (MH^+).

10



98

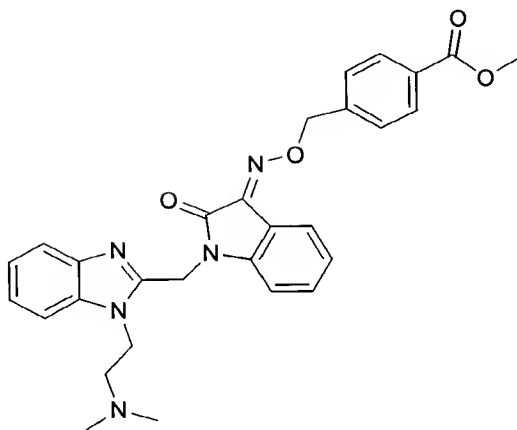
To a solution of compound **98b** (2.6 g, 14.6 mmol) in CH_2Cl_2 (50 mL) at -78°C was added compound **95e** (freshly prepared from **95b** (3.0g, 14.6 mmol) and thionyl chloride, 20 mL) in CH_2Cl_2 (50 mL). The mixture was stirred at -78°C for 1 hour then warmed to room temperature and stirred for 12 hours. The solvent was removed to give 2.8 g of a mixture of mono and diacetylated products. Both compounds can be converted to the desired product by heating the mixture in AcOH (100 mL) and concentrated HCl (2 mL) at reflux for 12 hours. The residue was purified by flash chromatography (gradient, $\text{CH}_2\text{Cl}_2:\text{MeOH} = 99:1$ to $\text{CH}_2\text{Cl}_2:\text{MeOH} = 97:3$) to give 1.8 g (68% yield) of compound **98** as a yellow solid:

^1H NMR ($\text{DMSO}-d_6$) δ 2.11 (s, 6 H), 2.58 (t, $J = 6.0$ Hz, 2 H), 4.39 (t, $J = 6.0$ Hz, 2 H), 5.27 (s, 2 H), 7.11-7.26 (m, 4 H), 7.54-7.65 (m, 4 H);

MS m/e 348 (MH^+);

Anal. Calcd for $\text{C}_{20}\text{H}_{20}\text{N}_4\text{O}_2 \cdot 0.7 \text{H}_2\text{O} \cdot 0.5 \text{AcOH}$: C, 64.50; H, 6.03; N, 14.33

Found: C, 64.68; H, 5.93; N, 14.32.

**99**

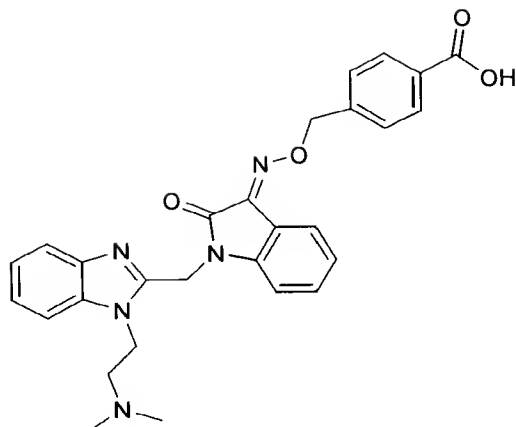
5 A mixture of compound **98** (200 mg, 0.57 mmol), compound **93b** (104 mg, 0.57 mmol) and *p*-toluenesulfonic acid (162 mg, 0.87 mmol) was stirred at reflux for 12 hours. The mixture was concentrated and the residue dissolved in EtOAc, washed with saturated NaHCO₃, dried over MgSO₄, and concentrated. The dark residue was purified by preparative HPLC (gradient, 80%MeOH/water
10 to 100% MeOH/water) to give 128 mg (44% yield) of compound **99** as a dark oil:

¹H NMR (DMSO-d₆) δ 2.95 (s, 6 H), 3.50-3.70 (m, 2 H), 3.86 (s, 3 H), 4.72-4.77 (m, 2 H), 3.38 (s, 2 H), 5.62 (s, 2 H), 7.10-7.27 (m, 4 H), 7.44-7.49 (m, 1 H), 7.58-7.63 (m, 3 H), 7.63-7.69 (d, J = 8.0 Hz, 1 H), 7.98-8.03 (m, 3 H);

15 MS m/e 511 (MH⁺);

Anal. Calcd for C₂₉H₂₉N₅O₄•0.4 H₂O: C, 46.29; H, 3.56; N, 7.38

Found: C, 46.29; H, 3.72; N, 7.49.

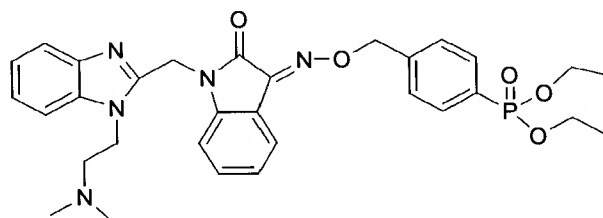
**100**

A solution of compound **99** in aqueous 1N HCl (50 mL) was heated to reflux for 6 hours then cooled and concentrated. The residue was purified by preparative HPLC (C18, gradient, 50-70%MeOH/water) to give a yellow solid. The solid was dissolved in 4N HCl in dioxane (10 mL). The solvent and excess HCl were evaporated to give 95 mg (75% yield) of compound **100** as a hydrochloride salt:

¹H NMR (DMSO-d₆) δ 2.90 (s, 6 H), 3.60-3.70 (m, 2 H), 5.00-5.03 (m, 2 H), 5.62 (s, 2 H), 5.66 (s, 2 H), 7.18 (t, J = 7.6 Hz, 1 H), 7.9 (d, J = 7.9 Hz, 1 H), 7.44-7.54 (m, 3 H), 7.60 (d, J = 8.2 Hz, 2 H), 7.69 (d, J = 8.0 Hz, 1 H), 7.99-8.03 (m, 3 H), 8.10 (d, J = 8.2 Hz, 1 H);

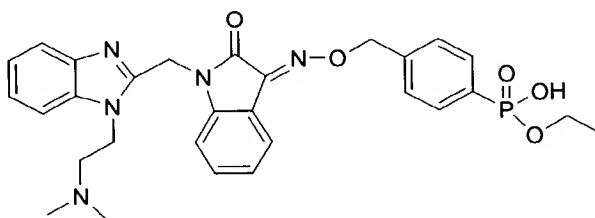
MS m/e 497 (MH⁺);

Anal. Calcd for C₂₈H₂₇N₅O₄•2.9 H₂O•1.8 HCl: C, 54.74; H, 5.67, N, 11.40
Found: C, 54.98; H, 5.27; N, 11.00.

**101**

Compound **101** was prepared using the same method as compound **99** with compound **88f**:

¹H NMR (DMSO-d₆) δ 1.23 (t, J = 7.0 Hz, 6 H), 2.91 (d, J = 4.8 Hz, 6 H), 3.57 (s, 2 H), 3.97-4.04 (m, 4 H), 4.86 (t, J = 7.4 Hz, 2 H), 5.47 (s, 2 H), 5.62 (s, 2 H), 7.17 (t, J = 7.7 Hz, 1 H), 7.25 (d, J = 8.0 Hz, 1 H), 7.30 (t, J = 7.7 Hz, 1 H), 7.39 (t, J = 7.4 Hz, 1 H), 7.45-7.49 (m, 1 H), 7.59-7.65 (m, 3 H), 7.72-7.80 (m, 2 H), 7.86 (d, J = 7.9 Hz, 1 H), 8.01 (t, J = 7.7 Hz, 1 H); MS m/e 590 (MH⁺).

**102**

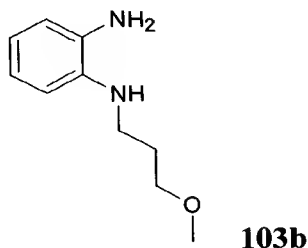
Compound **102** was prepared using the same procedure as compound **89** with compound **101**:

¹H NMR (DMSO-d₆) δ 1.09 (t, J = 7.0 Hz, 3 H), 3.00-3.10 (m, 2 H), 3.38 (bs, 6 H), 3.71-3.77 (m, 2 H), 4.55-4.70 (m, 2 H), 5.27 (s, 2 H), 5.50 (s, 2 H), 7.10 (t, J = 7.6 Hz, 1 H), 7.11-7.21 (m, 2 H), 7.23 (t, J = 7.1 Hz, 1 H), 7.40 (t, J = 6.7 Hz, 1 H), 7.41-7.47 (m, 2 H), 7.54 (d, J = 8.0 Hz, 1 H), 7.63 (d, J = 8.1 Hz, 1 H), 7.68-7.72 (m, 2 H), 7.92 (d, J = 6.9 Hz, 1 H).

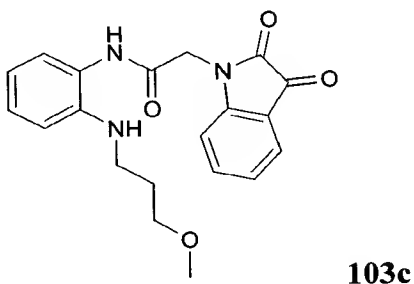
**103a**

To a mixture of 2-methoxypropylamine (8.45 g, 94.83 mmol) and potassium carbonate (26.21 g, 189.66 mmol) in CH₂Cl₂ (150 mL) was added 1-fluoro-2-nitrobenzene (13.38 g, 94.83 mmol) dropwise. The resulting mixture was stirred at 65 °C for 20 hours. The potassium carbonate was removed by filtration. The filtrate was washed with water and saturated aqueous sodium chloride, dried over MgSO₄, and evaporated to give 19.6 g (98% yield) of intermediate **103a** as an orange oil:

¹H NMR (CDCl₃) δ 1.95-2.00 (m, 2 H), 3.37 (s, 3 H), 3.39-3.43 (m, 2 H), 3.52 (t, J = 5.7 Hz, 2 H), 6.60 (dt, J = 1.2, 8.0 Hz, 1 H), 6.85 (d, J = 1.4, 7.0 Hz, 1 H), 8.14 (dd, J = 1.4, 7.0 Hz, 1 H), 8.28 (bs, 1 H).



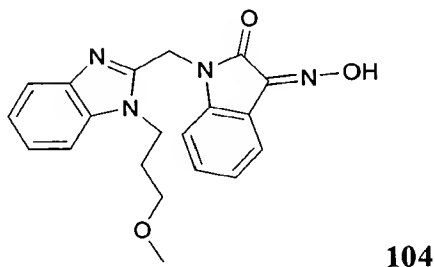
A mixture of **103a** (5.87 g, 27.92 mmol) and 10% palladium on carbon (1.17 g) in MeOH (100 mL) was hydrogenated at 50 psi for 4 hours. The catalyst was removed by filtration through a pad of celite. The filtrate was evaporated to give 4.59 g (91% yield) of the diamine **103b**.



To a mixture of diamine **103b** (3.45 g, 19.14 mmol) and DIEA (4.95 g, 38.30 mmol) in anhydrous THF (75 mL) was added a solution of compound **95e**

(4.28 g, 19.14 mmol) in THF (50 mL) slowly over 15 minutes. The resulting mixture was stirred for 10 minutes at room temperature. The solvent was evaporated to give the intermediate **103c** which was used without further purification.

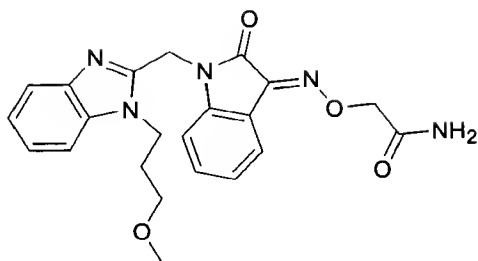
5



A mixture of compound **103c** (7.00 g, 19.0 mmol) and hydroxylamine hydrochloride (1.46 g, 21.0 mmol) in glacial acetic acid (150mL) was stirred at
10 120 °C for 30 minutes. The mixture was then concentrated *in vacuo* to a yellow solid. The crude solid was triturated with cold CH₂Cl₂ and isolated by filtration. The solid was redissolved in EtOAc and washed three times with saturated aqueous NaHCO₃ and then with brine. The organic phase was dried over
15 solid precipitated from solution. The resulting suspension was chilled in an ice bath and filtered to give 3.84 g (55% yield) of compound **104** as a light yellow fluffy powder:

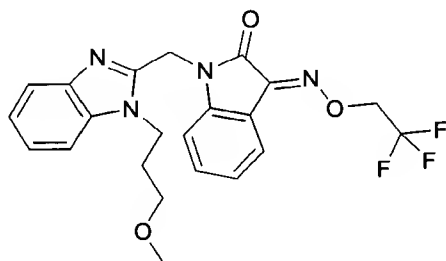
¹H NMR (acetone-d₆) δ 2.81 (s, 2 H), 3.30 (s, 3 H), 3.35 (t, J = 5.9 Hz, 2 H), 4.48
20 (t, J = 7.1 Hz, 2H), 5.33 (s, 2 H), 7.09-7.12 (m, 1 H), 7.18-7.21 (m, 1 H), 7.23-7.27 (m, 1 H), 7.33 (d, J = 7.80 Hz, 1 H), 7.37-7.41 (m, 1 H), 7.51 (d, J = 8.0 Hz, 1 H), 7.58 (d, J = 8.0 Hz, 1 H), 8.11 (d, J = 7.5 Hz, 1 H), 12.65 (s, 1 H);
MS m/e 365 (MH⁺).

118

**105**

Compound **104** (219 mg, 0.60 mmol) and 2-chloro-N-(hydroxymethyl)-
acetamide (148 mg, 1.2 mmol) were dissolved in anhydrous CH₃CN (50 mL). To
5 the solution was added BEMP on polystyrene (Fluka, 1.0 g, 1.8 mmol), and the
mixture was stirred at 60 °C overnight. To the resulting mixture was added PS-
thiophenol resin (Argonaut, 1.0 g, 1.2 mmol), MP-carbonate resin (Argonaut, 400
mg, 1.2 mmol) and triethylamine (36 mg, 0.36 mmol) and the mixture was heated
to 60 °C for 4 hours. The mixture was filtered to remove all resins and
10 concentrated *in vacuo* to afford 136 mg (54% yield) of compound **105** as a yellow
powder:

¹H NMR (DMSO-d₆) δ 2.00 (t, J = 6.4 Hz, 2 H), 3.25 (s, 3 H), 3.32 (t, J = 5.8 Hz,
2 H), 4.38 (t, J = 6.9 Hz, 2 H), 4.84 (s, 2 H), 5.28 (s, 2 H), 7.11-7.19 (m, 3 H),
15 7.22-7.25 (m, 1 H), 7.39 (s, 1 H), 7.43-7.47 (m, 1 H), 7.49 (s, 1 H), 7.53-7.57 (m,
2 H), 8.01 (d, J = 7.1 Hz, 1 H);
MS m/e 422 (MH⁺).

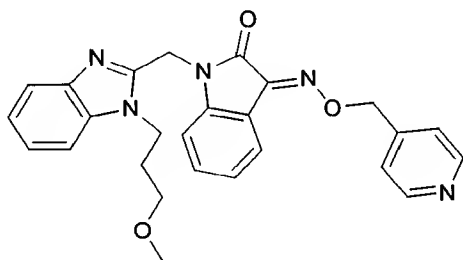
**106**

20

Compound **104** (219 mg, 0.60 mmol) and 2,2,2-trifluoroethyl-*p*-tosylate
(305 mg, 1.2 mmol) were combined in anhydrous CH₃CN (50 mL). To the

solution was added BEMP on polystyrene (Fluka, 1.0 g, 1.8 mmol) and the mixture was stirred at 60 °C overnight. To the resulting mixture was added PS-thiophenol resin (Argonaut, 1.0 g, 1.2 mmol), MP-carbonate resin (Argonaut, 400 mg, 1.2 mmol) and triethylamine (36 mg, 0.36 mmol), and the mixture was
5 heated to 60 °C for 4 hours. The mixture was filtered to remove all resins and concentrated *in vacuo*. The crude residue was dissolved in minimum CH₂Cl₂ and was diluted with diethyl ether (15 mL) and hexanes (30 mL). The resulting solution was concentrated *in vacuo* to a volume of 35 mL when solids precipitated from solution. The suspension was chilled in an ice bath, filtered and
10 rinsed with hexanes to give 140 mg (52% yield) of compound **106** as a canary yellow powder:

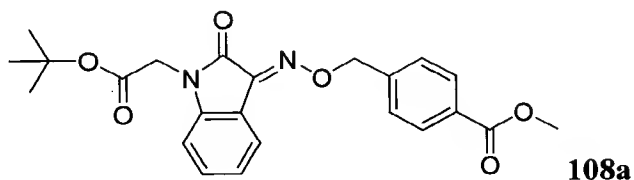
¹H NMR (DMSO-d₆) δ 1.99 (t, J = 6.5 Hz, 2 H), 3.24 (s, 3 H), 3.31 (t, J = 5.9 Hz, 2 H), 4.37 (t, J = 7.0 Hz, 2 H), 5.19 (q, J = 9.0 Hz, 2 H), 5.28 (s, 2 H), 7.21 (m, 4
15 H), 7.49 (m, 1 H), 7.55 (m, 2 H), 7.92 (d, J = 7.0 Hz, 1 H);
MS m/e 447 (MH⁺).

**107**

20 Compound **107** was prepared by the same procedure as described for the preparation of compound **105** with 4-(chloromethyl)pyridine hydrochloride. The crude product was purified by silica gel flash chromatography (CH₂Cl₂:CH₃OH = 40:1) to give 94 mg (34% yield) of compound **107** as a yellow solid:

25 ¹H NMR (DMSO-d₆) δ 1.98 (t, J = 6.5 Hz, 2 H), 3.22 (s, 3 H), 3.28 (t, J = 5.9 Hz, 2 H), 4.36 (t, J = 7.0 Hz, 2 H), 5.27 (s, 2 H), 5.59 (s, 2 H), 7.13-7.25 (m, 4 H),

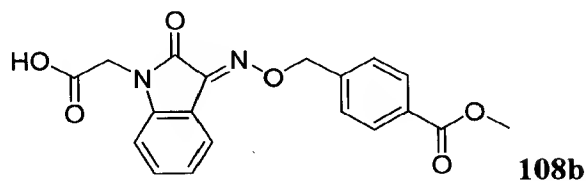
7.43-7.50 (m, 3 H), 7.54 (t, $J = 8.9$ Hz, 2H), 8.02 (d, $J = 7.0$ Hz, 1 H), 8.61-8.62 (m, 2 H);
MS m/e 456 (MH^+).



5

A mixture of compound **95a** (3.00 g, 11.23 mmol), compound **93b** (2.14 g, 11.79 mmol), and *p*-toluenesulfonic acid (427 mg, 2.25 mmol) in MeOH (50 mL) was stirred for 1.5 hours at room temperature. The mixture was
10 concentrated and the resulting yellow precipitate was filtered and dried to give 4.45 g (93% yield) of compound **108a**:

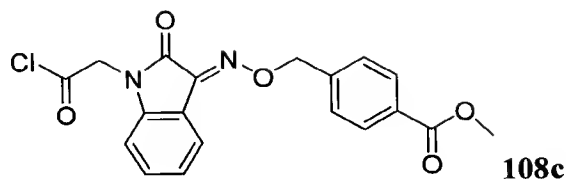
1H NMR ($CDCl_3$) δ 1.40 (s, 9 H), 3.85 (s, 3 H), 4.50 (s, 2 H), 5.59 (s, 2 H), 7.09-7.14 (m, 2 H), 7.48 (t, $J = 7.8$ Hz, 1 H), 7.59 (d, $J = 8.2$ Hz, 2 H), 7.95 (d, $J = 7.4$ Hz, 1 H), 7.99 (d, $J = 8.2$ Hz, 2 H).
15



Acid **108b** was prepared using the same procedure as compound **95b** with
20 compound **108a**:

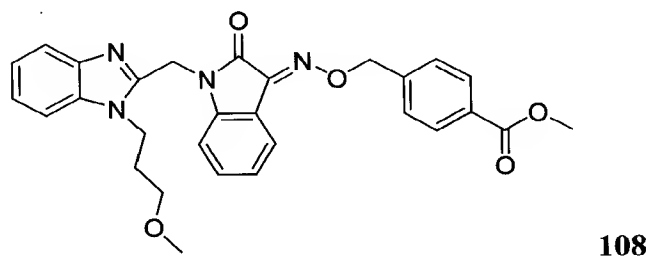
1H NMR ($CDCl_3$) δ 3.85 (s, 3 H), 4.50 (s, 2 H), 5.60 (s, 2 H), 7.11-7.14 (m, 2 H), 7.48 (dt, $J = 1.1, 7.8$ Hz, 1 H), 7.59 (d, $J = 8.2$ Hz, 2 H), 7.95 (d, $J = 6.8$ Hz, 1 H), 8.00 (d, $J = 8.3$ Hz, 2 H).

121



Compound **108c** was prepared using the same procedure as compound **95e** with compound **108b** and was used directly upon isolation.

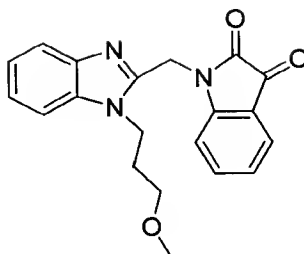
5



To a mixture of compound **103b** (233 mg, 1.29 mmol) and poly(4-vinylpyridine) (PVP, 2% cross-linked, 411 mg) in CH_2Cl_2 (15 mL) was added compound **108c** (500 mg, 1.29 mmol). The reaction mixture was stirred at room temperature for 16 hours. The PVP was removed by filtration and washed with CH_2Cl_2 . The filtrate was concentrated to a minimal amount of solvent and was then diluted with Et_2O . The brown precipitate was collected by filtration. The brown solid (463 mg) was dissolved in AcOH (10 mL) and stirred at 120 °C for 1 hour. The solvent was evaporated. The residue was dissolved in the minimal amount of MeOH and diluted with Et_2O . The yellow solid was collected by filtration to give 434 mg (82% yield over two steps) of compound **108**:

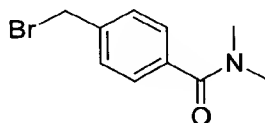
^1H NMR ($\text{DMSO}-d_6$) δ 1.96-1.99 (m, 2 H), 3.22 (s, 3 H), 3.28 (t, $J = 5.85$, 2 H), 3.85 (s, 3 H), 4.36 (t, $J = 7.0$ Hz, 2 H), 5.27 (s, 3 H), 5.62 (s, 3 H), 7.12 (t, $J = 7.8$ Hz, 2 H), 7.17 (t, $J = 7.2$ Hz, 2 H), 7.25 (t, $J = 7.5$ Hz, 1 H), 7.45 (t, $J = 7.8$ Hz, 1 H), 7.54 (t, $J = 9.4$ Hz, 2 H), 7.61 (d, 8.2 Hz, 2 H), 7.97 (d, 7.6 Hz, 1 H), 8.01 (d, $J = 8.2$ Hz, 2 H);
MS m/e 531 (MH^+).

122

**109a**

A solution of compound **103c** (850 mg, 2.31 mmol) in AcOH (10 mL) was stirred at 120 °C for 1 hour and then at room temperature for 18 hours. The solvent was concentrated and the brown residue was dissolved in CH₂Cl₂. To this solution was added Et₂O and the resulting brown precipitate was filtered. The solid was subjected to flash column chromatography (CH₂Cl₂/MeOH, 50:1) to give 589 mg (73% yield) of compound **109a**:

¹H NMR (CDCl₃) δ 1.94-1.99 (m, 2 H), 3.28 (t, J = 5.7 Hz, 2 H), 3.29 (s, 3 H), 4.36 (t, J = 7.2 Hz, 2 H), 5.27 (s, 2 H), 7.11 (t, J = 7.6 Hz, 1 H), 7.27-7.32 (m, 2 H), 7.39-7.41 (m, 1 H), 7.47 (d, J = 8.2 Hz, 1 H), 7.52-7.56 (m, 1 H), 7.61 (d, J = 7.6 Hz, 1 H), 7.77-7.79 (m, 1 H).

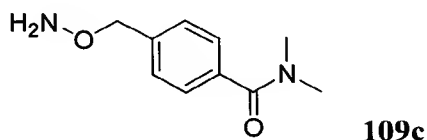
**109b**

To a solution of α-bromo-*p*-toluic acid (25 g, 116.25 mmol) in CH₂Cl₂ (200 mL) was added oxalyl chloride (17.71 g, 139.50 mmol) slowly followed by DMF (450 μL). The reaction was stirred approximately 1 hour until the solution became clear. The solvent was evaporated and the white solid was dried under vacuum to give the acid chloride. A mixture of the acid chloride (7.0 g, 30.24 mmol), poly(4-vinylpyridine) (PVP, 2% cross-linked, 9.6 g), and dimethylamine (2 M in THF, 15.9 mL, 31.75 mmol) in THF (200 mL) were stirred at room temperature for 15 hours. The poly(4-vinylpyridine) was removed by filtration

and the filtrate was concentrated to give 7.3 g (99% yield) of compound **109b** as a yellow solid:

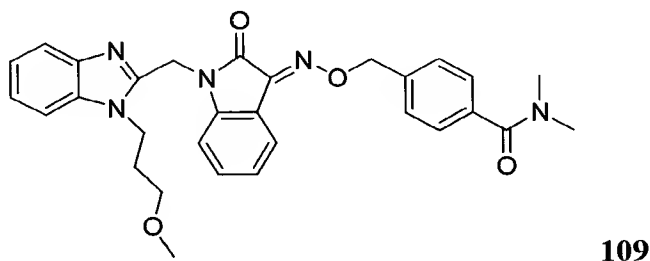
^1H NMR (CDCl_3) δ 2.99 (s, 3 H), 3.09 (s, 3 H), 4.48 (s, 2 H), 7.38-7.43 (m, 4 H).

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Compound **109c** was prepared using the same procedure as compound **88f** starting with compound **109b**.

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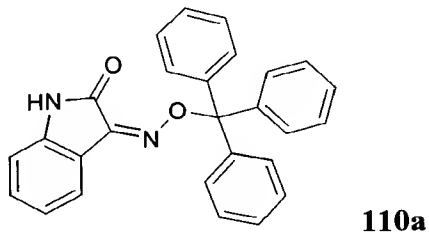


Compound **109** was prepared using the same procedure as compound **88** with compounds **109a** and **109c**:

15

^1H NMR (CDCl_3) δ 2.04-2.07 (m, 2 H), 3.00 (s, 3 H), 3.13 (s, 3 H), 3.30 (s, 3 H), 3.37 (t, J = 5.3 Hz, 2 H), 4.64 (t, J = 6.7 Hz, 2 H), 5.55 (s, 2 H), 5.66 (s, 2 H), 7.10 (t, J = 7.3 Hz, 1 H), 7.39-7.50 (m, 5 H), 7.52-7.56 (m, 2 H), 7.58-7.62 (m, 2 H), 7.94 (d, J = 7.5 Hz, 1 H), 7.98 (d, J = 7.5 Hz, 1 H).

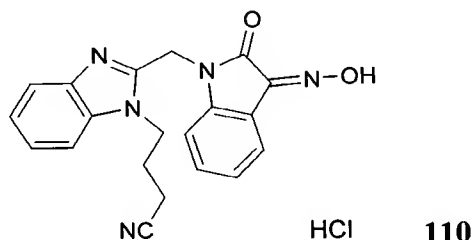
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Isatin (2.43 g, 16.50 mmol), *O*-tritylhydroxylamine (95%, 4.54 g, 16.5 mmol) and 1N aqueous HCl (1.7 mL, 1.70 mmol) were combined in a mixture of 100% ethanol (100 mL) and water (30 mL) and the mixture was stirred at room temperature for 1.5 hours. The reaction mixture gradually changed from a deep red color to yellow. After addition of NaHCO₃ (157 mg, 1.87 mmol) to neutralize the HCl, the suspension was chilled in an ice bath and filtered to isolate a yellow powder. Heating the powder at 110 °C under vacuum overnight gave 5.63 g (84% yield) of compound **110a** as a canary yellow powder:

¹H NMR (CDCl₃) δ 6.86 (d, J = 7.8 Hz, 1 H), 7.06-7.09 (m, 1H), 7.25-7.38 (m, 16 H), 7.94 (s, 1 H), 8.18 (d, J = 7.6 Hz, 1 H);

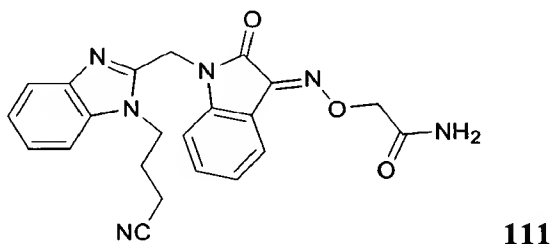
MS m/e 427 (M+Na⁺).



A mixture of compound **110a** (3.00 g, 7.42 mmol), compound **25b** (2.00 g, 7.42 mmol) and Cs₂CO₃ (7.25g, 22.3 mmol) in anhydrous CH₃CN (70 mL) was stirred at reflux for 2 hours. The mixture was cooled to room temperature, diluted with EtOAc, and washed with water. The organic layer was dried over anhydrous MgSO₄ and concentrated *in vacuo* to a yellow oil. The crude product was dissolved in a minimum of CH₂Cl₂ and diluted with 15 volumes of MeOH while swirling. Solids precipitated from solution. The suspension was chilled in an ice bath, filtered, rinsed with ice-cold methanol, and allowed to air-dry to give the trityl oxime adduct. A solution of this intermediate (2.00 g, 3.32 mmol) in 1,4-dioxane (50 mL) was treated with 4N HCl in dioxane (8.3 mL, 33.2 mmol) and stirred at room temperature for 3 hours. The reaction mixture was filtered to isolate 1.19 g (88% yield) of compound **110** as a fluffy yellow solid:

^1H NMR (DMSO- d_6) δ 2.20 (t, J = 7.4 Hz, 2 H), 2.70 (t, J = 7.4 Hz, 2 H), 4.54 (t, J = 7.3 Hz, 2 H), 5.52 (s, 2 H), 7.15 (t, J = 7.5 Hz, 1 H), 7.19 (d, J = 8.0 Hz, 1 H), 7.41-7.48 (m, 3 H), 7.65 (d, J = 8.0 Hz, 1 H), 7.87 (d, J = 7.5 Hz, 1 H), 8.08 (d, J = 7.3 Hz, 1 H), 13.65 (s, 1 H);

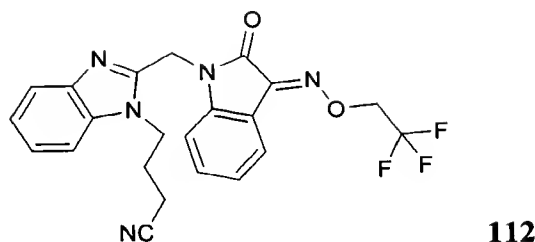
5 MS m/e 360 (MH^+).



Compound **110** (317 mg, 0.80 mmol) and 2-chloro-N-(hydroxymethyl)-
 10 acetamide (198 mg, 1.6 mmol) were dissolved in anhydrous CH_3CN (35 mL). To
 the solution was added BEMP on polystyrene (Fluka, 1.2 g, 2.4 mmol), and the
 mixture was stirred at 60°C overnight. To the resulting mixture was added PS-
 thiophenol resin (Argonaut, 1.2 g, 1.6 mmol), MP-carbonate resin (Argonaut, 513
 mg, 1.6 mmol) and triethylamine (36 mg, 0.36 mmol) and the mixture was heated
 15 to 60°C for 6 hours. The mixture was filtered to remove all resins and
 concentrated *in vacuo* to afford 201 mg (60% yield) of compound **111** as a yellow
 powder:

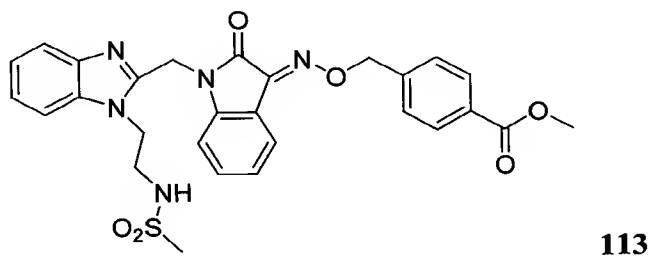
^1H NMR (DMSO- d_6) δ 2.13 (t, J = 7.5 Hz, 2 H), 2.64 (t, J = 7.4 Hz, 2 H), 4.40 (t,
 20 J = 7.5 Hz, 2 H), 4.84 (s, 2 H), 5.31 (s, 2 H), 7.12-7.21 (m, 3 H), 7.24-7.27 (m, 1
 H), 7.38 (s, 1 H), 7.44-7.49 (m, 2 H), 7.56 (d, J = 8.0 Hz, 1 H), 7.61 (d, J = 8.0
 Hz, 1 H), 8.02 (d, J = 7.5 Hz, 1 H);
 MS m/e 417 (MH^+).

126



Compound **110** (317 mg, 0.80 mmol) and 2,2,2-trifluoroethyl-*p*-tosylate (407 mg, 1.6 mmol) were dissolved in anhydrous CH₃CN (35 mL). To the solution was added BEMP on polystyrene (Fluka, 1.2 g, 2.40 mmol), and the mixture was stirred at 60 °C overnight. To the resulting mixture was added PS-thiophenol resin (Argonaut, 1.2 g, 1.60 mmol), MP-carbonate resin (Argonaut, 513 mg, 1.60 mmol) and triethylamine (36 mg, 0.36 mmol), and the mixture was heated to 60 °C for 6 hours. The mixture was filtered to remove all resins and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (CH₂Cl₂:CH₃OH = 100:1) to give 224 mg (63% yield) of compound **112** as a yellow solid:

¹H NMR (DMSO-*d*₆) δ 2.13 (t, *J* = 7.5 Hz, 2 H), 2.64 (t, *J* = 7.4 Hz, 2 H), 4.40 (t, *J* = 7.6 Hz, 2 H), 5.19 (q, *J* = 9.0 Hz, 2 H), 5.31 (s, 2 H), 7.17 (t, *J* = 7.6 Hz, 2 H), 7.23-7.27 (m, 2 H), 7.49-7.52 (m, 1 H), 7.55 (d, *J* = 8.0 Hz, 1 H), 7.61 (d, *J* = 8.0 Hz, 1 H), 7.92 (d, *J* = 7.5 Hz, 1 H); MS *m/e* 442 (MH⁺).

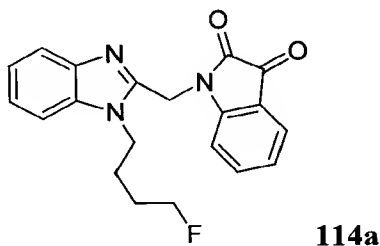


Compound **113** was prepared using the same procedure as compound **108** with compound **108c** and compound **23e**:

^1H NMR (DMSO- d_6) δ 2.81 (s, 3 H), 3.42 (t, J = 5.8 Hz, 2 H), 3.86 (s, 3 H), 4.66 (t, J = 5.4 Hz, 2 H), 5.34 (s, 2 H), 5.63 (s, 2 H), 7.12-7.19 (m, 3 H), 7.27 (t, J = 7.3 Hz, 1 H), 7.40-7.45 (m, 2 H), 7.53 (d, J = 8.0 Hz, 1 H), 7.63 (d, J = 8.3 Hz, 2 H), 7.99 (d, J = 7.3 Hz, 1 H), 8.02 (d, J = 8.3 Hz, 2 H);

5 NEW Spectral DATA

1-[1-(4-Fluoro-butyl)-1H-benzoimidazol-2-ylmethyl]-1H-indole-2,3-dione



10

1-[1-(4-Fluoro-butyl)-1H-benzoimidazol-2-ylmethyl]-1H-indole-2,3-dione was prepared as described for compound 25 starting from isatin (1.54 g, 10.5 mmol) and **159c** (2.90 g, 10.5 mmol). The product was obtained by precipitation from diethyl ether and methylene chloride to give 1-[1-(4-fluoro-butyl)-1H-benzoimidazol-2-ylmethyl]-1H-indole-2,3-dione (385 mg, 10%) as a yellow solid.

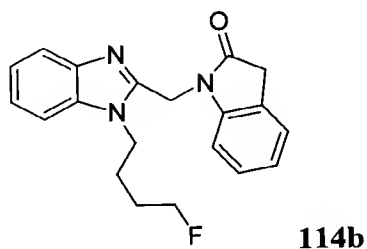
15

^1H NMR (CDCl_3) δ 7.79 (d, J 8.0 Hz, 1H), 7.60 (m, 3H), 7.34 (m, 3H), 7.13 (t, J 7.4 Hz, 1H), 5.28 (s, 2H), 4.46 (dt, J 5.6, 47 Hz, 2H), 4.33 (t, J 7.5 Hz, 2H), 1.82 (m, 4H);

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MS m/e 352 (MH^+).

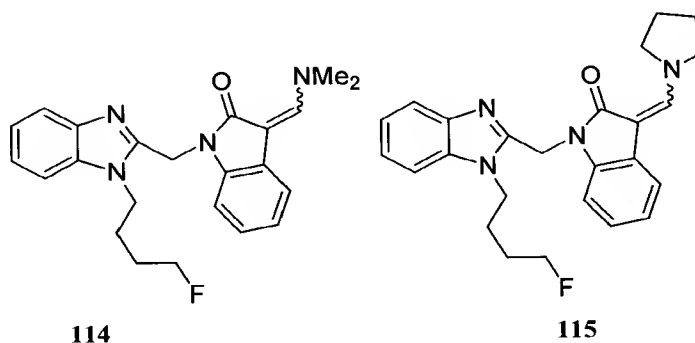
1-[1-(4-Fluoro-butyl)-1H-benzoimidazol-2-ylmethyl]-1,3-dihydro-indol-2-one



A suspension of 1-[1-(4-Fluoro-butyl)-1H-benzimidazol-2-ylmethyl]-1H-indole-2,3-dione (607 mg, 1.73 mmol) in hydrazine hydrate (15 mL) was heated at reflux for 18 min. The solution was cooled to room temperature and quenched with ice and ethyl acetate (40 mL). The layers were separated and the aqueous phase extracted with ethyl acetate (2x40 mL). The combined organic phases were washed with brine and dried (MgSO₄). The product was purified by flash column chromatography (eluent 3% methanol in methylene chloride) to give compound **114b** 325 mg, 56% as an off white solid.

¹H NMR (CDCl₃) δ 7.80 (dd, J 1.9, 5.3 Hz, 1H), 7.43 (d, J 8.0 Hz, 1H), 7.29 (m, 5H), 7.02 (t, J 7.5 Hz, 1H), 5.27 (s, 2H), 4.45 (dt, J 4.9, 47 Hz, 2H), 4.32 (t, J 7.2 Hz, 2H), 3.61 (s, 2H), 1.78 (m, 4H);

MS m/e 338 (MH⁺).

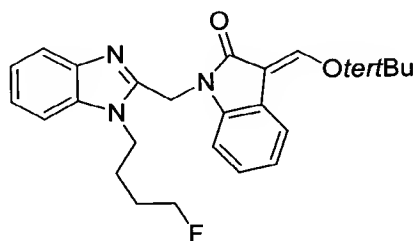


To a solution of the oxindole **114b** (26 mg, 0.078 mmol) in DMF (2.5 mL) was added DMF neopentyl acetal (327 μL, 1.17 mmol). The solution was stirred for 1 hour at room temperature. The volatiles were stripped off and the residue purified by flash column chromatography (eluent 3% methanol in methylene chloride). The slow moving product was the enamide **114** (10 mg, 33%) as a 2:1 mixture of geometric isomers (off white solid after trituration from diethyl ether). The fast moving product was the neopentyl enol ether, which was dissolved in methylene chloride and treated with a large excess of pyrrolidine at room temperature. After 2 hours, the volatiles were removed *in vacuo*, and the residue purified by flash column chromatography (eluent 3% methanol in

methylene chloride) to give 7 mg of the enamide **115** (3:1 mixture of geometric isomers) as an oil.

Compound **114**: ^1H NMR (CDCl_3) δ 7.80 (m, 1 H), 7.68 (s, 1H), 7.37 (d, J 7.9 Hz, 1H), 7.29 (m, 4H), 6.95 (m, 2H), 5.39 (s, 2H), 4.34 (m, 4H), 3.36 (s, 6H), 1.67 (m, 4 H);
MS m/e 393 (MH^+);

Compound **115**: ^1H NMR (CDCl_3) δ 7.84 (s, 1H), 7.79 (m, 1H), 7.49 (d, J = 7.7 Hz, 1H), 7.34 (d, J = 7.7 Hz, 1H), 7.27 (m, 3 H), 7.13 (d, J = 7.5 Hz, 1H minor isomer), 6.92 (m, 2H), 5.39, 5.38 (s, 2H), 4.30 (m, 4H), 3.83 (m, 4H), 2.04 (m, 4H), 1.66 (m, 4H);
MS m/e 419 (MH^+).



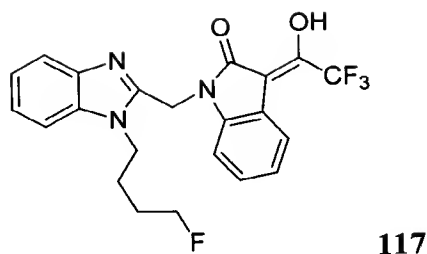
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A solution of the oxindole **114b** (36 mg, 0.11 mmol) and DMF *tert*-Bu acetal (323 mg, 1.59 mmol) in DMF (2 mL) was stirred at 0°C for 3 hours. The volatiles were removed *in vacuo*, and the residue purified by flash column chromatography (eluent 2%, 5% methanol in methylene chloride) to give 12 mg (fast moving product, 27%) of the enol ether **116** as a brownish oil. The slow moving product was the enamide **114** as a 2:1 mixture of geometric isomers (27 mg, 65%).

^1H NMR (CDCl_3) δ 7.93 (s, 1H), 7.79 (m, 1H), 7.61 (d, J 7.3 Hz, 1H), 7.28 (m, 4H), 7.11 (t, J = 7.4 Hz, 1H), 7.00 (t, J = 7.4 Hz, 1H), 5.31 (s, 2H), 4.35 (m, 4H), 1.68 (m, 4H), 1.53 (s, 9H);
MS m/e 422 (MH^+).

25

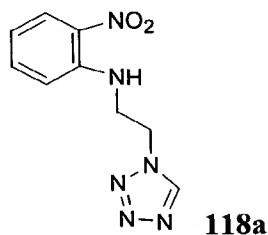
130



To a suspension of NaH (60% in mineral oil, 7.1 mg, 0.18 mmol) in THF (2 mL) was added the oxindole **114b** (40 mg, 0.12 mmol) under nitrogen. The mixture was heated at reflux temperature, and ethyl trifluoroacetate (21 μ L, 0.18 mmol) was added. After 2 hours of reflux the mixture was cooled to room temperature and poured into 1M aq. HCl. The product was extracted into ethyl acetate (2x15 mL). The combined organic extracts were washed with brine and dried (MgSO₄). The pure product **117** was obtained by precipitation from diethyl ether (20 mg, 38%) as a grey solid.

¹H NMR (DMSO) δ 7.98 (d, J = 7.5 Hz, 1H), 7.93 (d, J = 6.9 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.58 (m, 2H), 6.85 (m, 3H), 5.49 (s, 2H), 4.54 (br s, 2H), 4.35 (dt, J = 5.7, 47 Hz, 2H), 1.66 (m, 4H);

MS m/e 434 (MH⁺).



A mixture of amine **23c** (40 g, 220 mmol), trimethyl orthoformate (38.5 mL, 352 mmol) and sodium azide (15.7 g, 242 mmol) in acetic acid (400 mL) was heated to reflux for 12 hours. The resulting mixture was cooled to room temperature and poured into 1N HCl in ice (300 mL). The precipitate was filtered and recrystallized from EtOAc to give 19.2 g (37% yield) of compound **118a** as bright yellow needles:

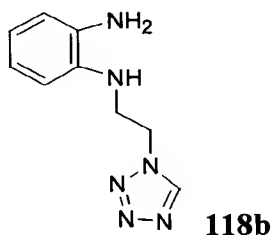
^1H NMR (DMSO- d_6) δ 3.90 (J = 6.6 Hz, 2 H), 4.73 (t, J = 6.6 Hz, 2 H), 6.72 (t, J = 6.9 Hz, 1H), 7.07 (d, J = 10.2 Hz, 1H), 7.53 (d, J = 6.3 Hz, 1H), 8.06 (d, J = 10.1 Hz, 1 H), 8.18 (t, J = 6.6 Hz, 1H); 9.40 (s, 1 H);

IR (KBr, cm^{-1}) 1621, 1514, 1347, 740;

5 MS m/e 235 (MH^+);

Anal. Calcd for $\text{C}_9\text{H}_{10}\text{N}_6\text{O}_2$: C, 46.15; H, 4.30; N, 35.88

Found: C, 46.17; H, 4.35; N, 35.85.



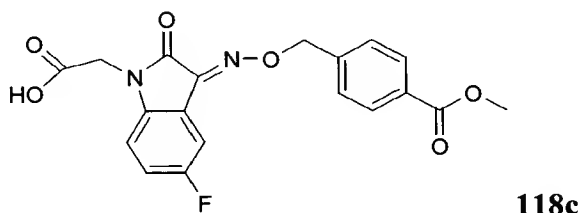
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A solution of compound **118a** (3.5 g, 14.95 mmol) in EtOH (50 mL) containing 10% palladium on carbon (200 mg) was hydrogenated at 50 psi for 4 hours. The reaction mixture was filtered and concentrated to give 2.8 g (93% yield) of compound **118b** as a black solid:

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^1H NMR (DMSO- d_6) δ 3.52 (q, J = 6.0, 2 H), 4.46 (s, 3 H), 4.63-4.69 (m, 3 H), 6.45-6.57 (m, 4 H), 9.4 (s, 1 H);

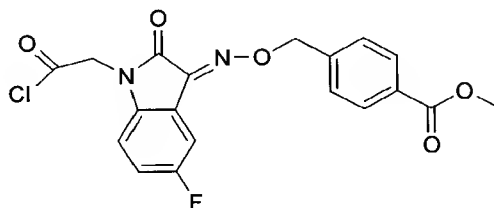
MS m/e 205 (MH^+).



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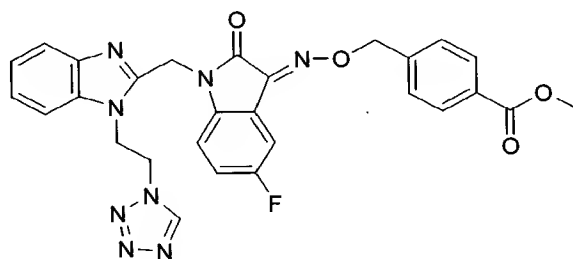
Compound **118c** was prepared using the same sequence of procedures as compound **108b** starting with 5-fluoroisatin.

^1H NMR (DMSO- d_6) δ 3.85 (s, 3 H), 4.50 (s, 2 H), 5.61 (s, 2 H), 7.18 (dd, J = 4.1, 8.7 Hz, 1 H), 7.60 (d, J = 8.2 Hz, 2 H), 7.75 (dd, J = 2.7, 8.1 Hz, 1 H), 7.99 (d, J = 8.2 Hz, 2 H).

**118d**

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Compound **118d** was prepared using the same procedure as compound **98c** with compound **118c** and was used immediately upon isolation.

**119**

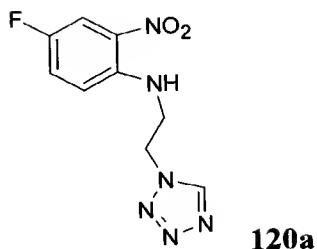
10

Compound **119** was prepared using the same procedure as compound **108** with compounds **118b** and **118d**:

^1H NMR (DMSO- d_6) δ 3.86 (s, 3 H), 4.88 (t, J = 5.8 Hz, 2 H), 5.02 (t, J = 5.9 Hz, 2 H), 5.12 (s, 2 H), 5.63 (s, 2 H), 7.12-7.19 (m, 2 H), 7.27-7.29 (m, 1 H), 7.35-7.39 (m, 1 H), 7.52-7.54 (m, 1 H), 7.63 (d, J = 8.3 Hz, 2 H), 7.77-7.79 (m, 1 H), 8.01 (d, J = 8.3 Hz, 2 H), 9.29 (s, 1 H);
MS m/e 555 (MH^+).

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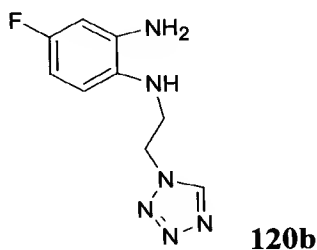
133



Compound **120a** was prepared using the same procedure as compound **118a** starting with 2,5-difluoronitrobenzene:

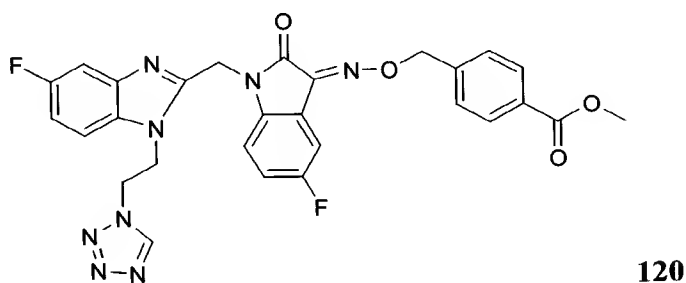
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^1H NMR (DMSO- d_6) δ 3.88-3.92 (m, 2 H), 4.70-4.72 (m, 2 H), 7.13-7.16 (m, 1 H), 7.50-7.54 (m, 1 H), 7.86-7.89 (m, 1 H), 8.12-8.15 (m, 1 H), 9.39 (m, 1H); MS m/e 252 (MH^+).



10

Diamine **120b** was prepared using the same procedure as compound **118b** with compound **120a** and was used directly upon isolation.

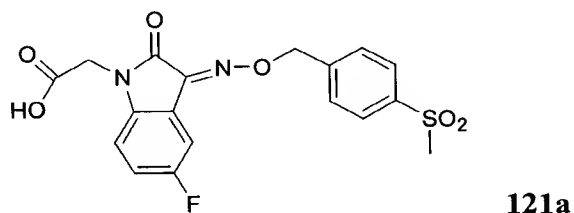


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Compound **120** was prepared using the same procedure as compound **108** with compounds **118d** and **120b**:

^1H NMR (DMSO- d_6) δ 3.23 (s, 3 H), 4.85-4.89 (m, 2 H), 5.01-5.03 (m, 2 H), 5.11 (s, 2 H), 5.63 (s, 2 H), 7.01-7.07 (m, 1 H), 7.11-7.16 (m, 1 H), 7.25-7.30 (m, 1 H), 7.36-7.38 (m, 2 H), 7.63 (d, J = 8.3 Hz, 2 H), 7.80-7.82 (m, 1 H), 8.01 (d, J = 8.3 Hz, 1 H), 9.30 (s, 1 H);

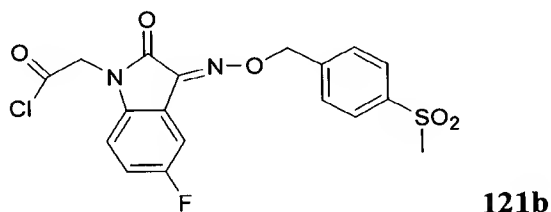
5 MS m/e 573 (MH^+).



10 Acid **121a** was prepared using the same sequence of procedures for compound **108b** starting with 5-fluoroisatin and compound **96a**:

^1H NMR (DMSO- d_6) δ 3.23 (s, 3 H), 4.51 (s, 2 H), 5.65 (s, 2 H), 7.19 (dd, J = 4.1, 8.7 Hz, 1 H), 7.40 (dt, J = 2.7, 8.9 Hz, 1 H), 7.73 (d, J = 8.4 Hz, 2 H), 7.81 (dd, J = 2.7, 8.1 Hz, 1 H), 7.97 (d, J = 8.4 Hz, 2 H).

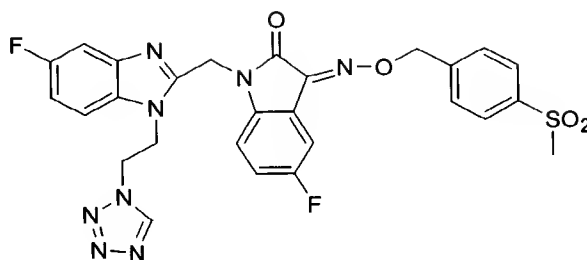
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Compound **121b** was prepared using the same procedure as compound **108c** with compound **121a** and was used directly upon isolation.

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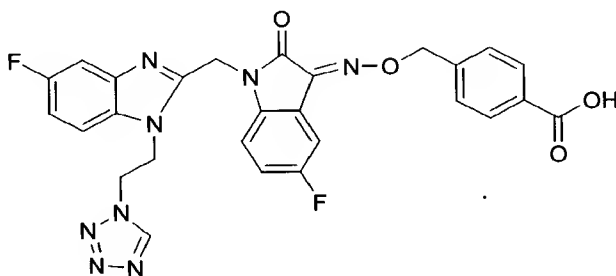
135

**121**

Compound **121** was prepared using the same procedure as compound **108** with compounds **120b** and **121b**:

- 5 ^1H NMR (DMSO- d_6) δ 3.23 (s, 3 H), 4.85-4.89 (m, 2 H), 5.01-5.03 (m, 2 H), 5.11 (s, 2 H), 5.66 (s, 2 H), 6.96-7.01 (m, 1 H), 7.01-7.07 (m, 1 H), 7.12-7.14 (m, 1 H), 7.26-7.33 (m, 1 H), 7.38-7.41 (m, 2 H), 7.75 (d, J = 8.3 Hz, 2 H), 7.79-7.82 (m, 1 H), 7.95-7.99 (m, 3 H), 9.29 (s, 1 H);
MS m/e 593 (MH^+).

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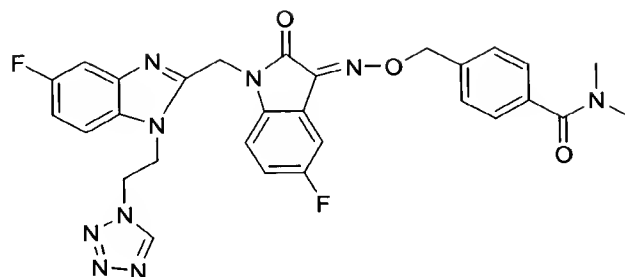
**122**

Compound **122** was prepared using the same procedure as compound **94** with methyl ester **120**:

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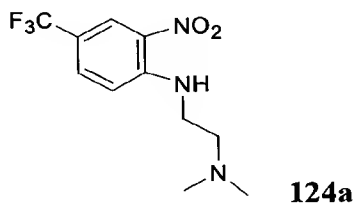
- ^1H NMR (DMSO- d_6) δ 4.40 (s, 1 H), 4.79-4.81 (m, 1 H), 4.88-4.91 (m, 2 H), 5.01-5.03 (m, 1 H), 5.12 (s, 1 H), 5.36 (s, 1 H), 5.62 (s, 2 H), 6.89-6.95 (m, 1 H), 6.99-7.17 (m, 1 H), 7.29-7.32 (m, 1 H), 7.35-7.39 (m, 1 H), 7.41-7.44 (m, 1 H), 7.60 (d, J = 8.2 Hz, 1 H), 7.77-7.79 (m, 1 H), 7.83 (d, J = 8.1 Hz, 1 H), 7.99 (d, J =
20 8.1 Hz, 2 H), 9.17 (s, 1 H), 9.30 (s, 1 H);
MS m/e 559 (MH^+).

136

**123**

To a solution of compound **122** (400 mg, 0.72 mmol), dimethylamine hydrochloride (87.6 mg, 1.07 mmol), and DIEA (185.1 mg, 1.43 mmol) in DMF (10 mL) was added bromotripyrrolidineophosphonium hexafluorophosphate (PyBroP[®], Fluka, 400.7 mg, 0.86 mmol). The resulting mixture was stirred at room temperature for 18 hours. The mixture was diluted with MeOH (1 mL) and the solvent was evaporated. The residue was dissolved in EtOAc and washed with 5% KHSO₄, 5% NaHCO₃, and brine. The organic layer was dried over Na₂SO₄ and concentrated to give 300 mg (72% yield) of compound **123** as a yellow solid:

¹H NMR (DMSO-d₆) δ 2.91 (s, 3 H), 2.98 (s, 3 H), 4.88-4.90 (m, 2 H), 5.01-5.03 (m, 2 H), 5.11 (s, 2 H), 5.58 (s, 2 H), 7.02-7.07 (m, 1 H), 7.14-7.17 (m, 1 H), 7.27-7.32 (m, 1 H), 7.33-7.39 (m, 2 H), 7.45 (d, J = 8.2 Hz, 2 H), 7.54 (d, J = 8.1 Hz, 2 H), 7.76-7.78 (m, 1 H), 9.30 (s, 1 H); MS m/e 586 (MH⁺).

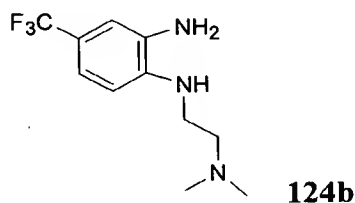
**124a**

20

Compound **124a** was prepared using the same procedure as compound **98a** with 4-fluoro-3-nitrobenzotrifluoride:

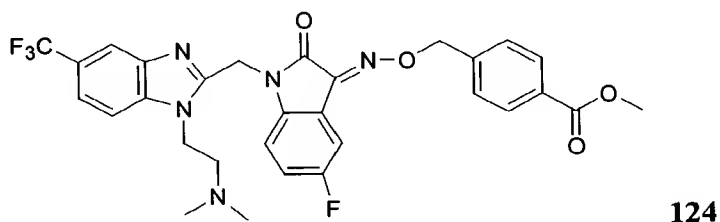
^1H NMR (DMSO- d_6) δ 2.22 (s, 6 H), 2.55 (t, J = 6.2 Hz, 2 H), 3.43-3.47 (m, 2 H), 7.22 (d, J = 8.8 Hz, 1 H), 7.81 (dd, J = 2.2, 9.2 Hz, 1 H), 8.32 (s, 1 H), 8.60 (t, J = 4.5 Hz, 1 H);
MS m/e 278 (MH^+).

5



Compound **124b** was prepared using the same procedure as compound **98b** with compound **124a** and was used directly upon isolation.

10

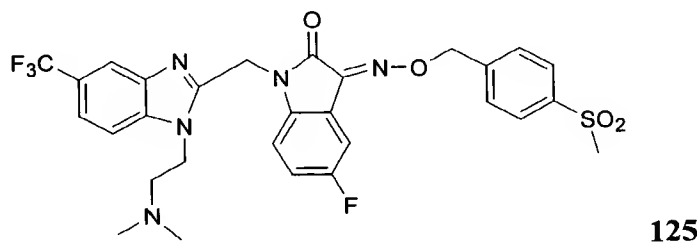


Compound **124** was prepared using the same procedure as compound **108** with compound **118d** and **124b**:

15

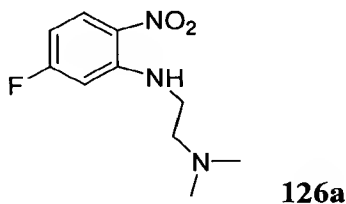
^1H NMR (DMSO- d_6) δ 2.50 (s, 6 H), 3.86 (s, 3 H), 4.75-4.85 (bs, 2 H), 5.41 (s, 2 H), 5.64 (s, 2 H), 5.58 (s, 2 H), 7.17-7.26 (m, 1 H), 7.37-7.39 (m, 1 H), 7.63 (d, J = 8.0 Hz, 3 H), 7.80-7.82 (m, 1 H), 7.88-7.96 (m, 1 H), 7.99-8.03 (m, 3 H);
MS m/e 598 (MH^+).

20



Compound **125** was prepared using the same procedure as compound **108** with compound **121b** and **124b**:

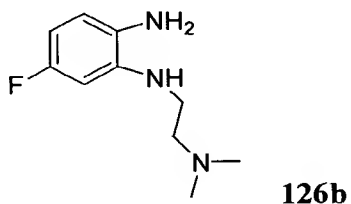
¹H NMR (DMSO-d₆) δ 2.90 (d, J = 4.8 Hz, 6 H), 3.24 (s, 3 H), 4.84-4.86 (m, 4 H), 5.44 (s, 2 H), 5.67 (s, 2 H), 7.24-7.27 (m, 1 H), 7.36-7.42 (m, 1 H), 7.63-7.64 (m, 1 H), 7.76 (d, J = 8.3 Hz, 2 H), 7.84-7.87 (m, 1 H), 7.98-8.00 (m, 4 H); MS m/e 618 (MH⁺).



10

Compound **126a** was prepared using the same procedure as compound **98a** with 2,4-difluoronitrobenzene:

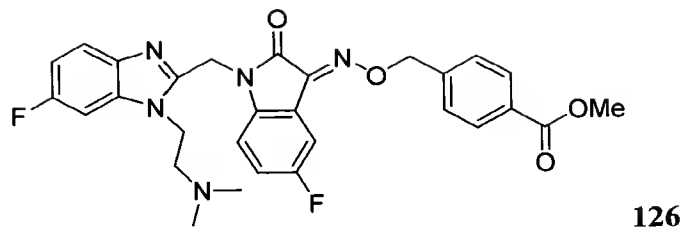
¹H NMR (CDCl₃) δ 2.21 (s, 6 H), 2.53 (t, J = 6.1 Hz, 2 H), 3.33-3.37 (m, 2 H), 6.51-6.56 (m, 1 H), 6.85 (dd, J = 2.7, 12.2 Hz, 1 H), 8.17 (dd, J = 6.3, 9.5 Hz, 1 H), 8.42 (bs, 1 H); MS m/e 228 (MH⁺).



20

Compound **126b** was prepared using the same procedure as compound **98b** with compound **126a** and was used immediately upon isolation.

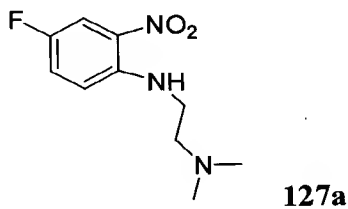
139



Compound **126** was prepared using the same procedure as compound **108** with compound **118d** and **126b**:

5

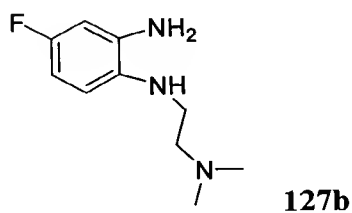
^1H NMR (CDCl_3) δ 2.94 (s, 6 H), 3.32 (bs, 2 H), 3.94 (s, 3 H), 4.97 (bs, 2 H), 5.28 (s, 2 H), 5.61 (s 2 H), 7.05 (t, $J = 13.6$ Hz, 1 H), 7.16 (dt, $J = 4.3, 14.5$ Hz, 1 H), 7.51 (d, $J = 13.5$ Hz, 3 H), 7.69-7.63 (m, 3 H), 8.08 (d, $J = 13.7$ Hz, 2 H).



10

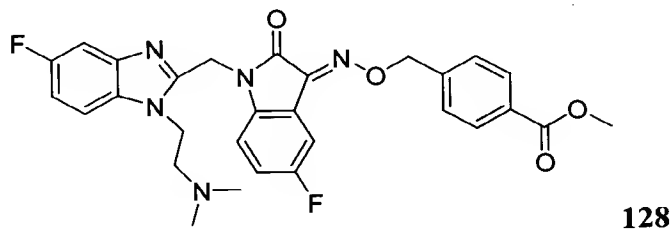
Compound **127a** was prepared using the same procedure as compound **98a** with 2, 5-difluoronitrobenzene:

15 ^1H NMR (DMSO-d_6) δ 2.21 (s, 6 H), 2.53 (t, $J = 6.05$ Hz, 2 H), 3.35-3.39 (m, 2 H), 7.08 (dd, $J = 4.8, 9.52$ Hz, 1 H), 7.50-7.55 (m, 1 H), 7.83 (dd, $J = 3.0, 9.5$ Hz, 1 H), 8.22 (bs, 1 H);
MS m/e 227 (MH^+).



20

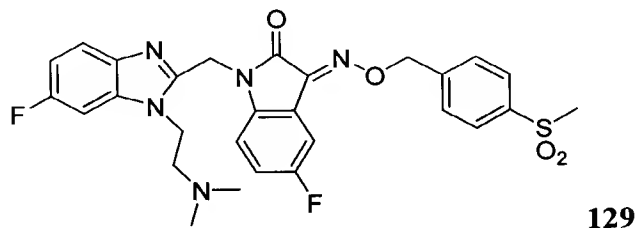
Compound **127b** was prepared using the same procedure as compound **98b** with compound **127a** and was used immediately upon isolation.



5

Compound **128** was prepared using the same procedure as compound **108** with compound **118d** and **127b**:

¹H NMR (CDCl₃) δ 2.94 (s, 6 H), 3.27-3.44 (m, 2 H), 3.93 (s, 3 H), 5.01 (m, 2 H), 5.29 (s, 2 H), 5.69 (s, 2 H), 7.15 (d, J = 9.6 Hz, 2 H), 7.41 (d, J = 12.4 Hz, 1 H), 7.50 (d, J = 12.6 Hz, 3 H), 7.67 (d, J = 9.5 Hz, 1 H), 7.88 (bs, 1 H), 8.07 (d, J = 12.1 Hz, 2 H).

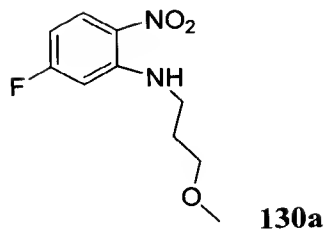


15

Compound **129** was prepared using the same procedure as compound **108** with compound **121b** and **126b**:

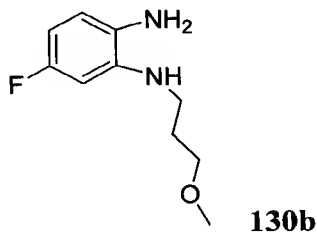
¹H NMR (DMSO-d₆) δ 2.85 (s, 6 H), 3.23 (s, 3 H), 3.52 (bs, 2 H), 4.76 (t, J = 7.5, 2 H), 5.36 (s, 2 H), 5.67 (s, 2 H), 7.05 (dt, J = 2.2, 9.0 Hz, 1 H), 7.26 (dd, J = 4.1, 8.7 Hz, 1 H), 7.39 (dt, J = 2.6, 9.1 Hz, 1 H), 7.57 (dd, J = 4.9, 8.7 Hz, 1 H), 7.71 (d, J = 9.4 Hz, 1 H), 7.75 (d, J = 8.2 Hz, 2 H), 7.84 (dd, J = 2.6, 8.0 Hz, 1 H), 7.98 (d, J = 8.2 Hz, 2 H).

141

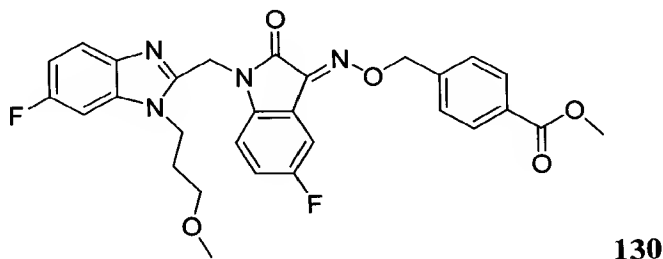


Compound **130a** was prepared using the same procedure as compound **103a** starting with 2,4-difluoronitrobenzene:

^1H NMR (CDCl_3) δ 1.89-2.04 (m, 2 H), 3.29, 3.28-3.44 (s over m, 5 H), 3.54 (t, J = 5.7 Hz, 2 H), 6.33-6.37 (m, 1 H), 6.52 (dd, J = 2.7, 11.5 Hz, 1 H), 8.22 (dd, J = 6.3, 9.5 Hz, 1 H), 8.44 (bs, 1 H).



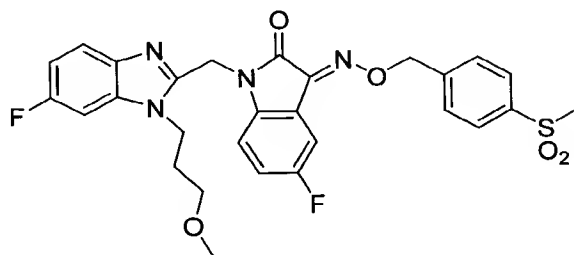
Compound **130b** was prepared using the same procedure as compound **103b** with compound **130a** and was used immediately upon isolation.



Compound **130** was prepared using the same procedure as compound **108** with compounds **118d** and **130b**:

^1H NMR (CDCl_3) δ 1.96-1.99 (m, 2 H), 2.12 (s, 3 H), 3.32 (s, 3 H), 3.32 (t, J = 9.0 Hz, 2 H), 3.94 (s, 3 H), 4.38 (t, J = 11.6 Hz, 2 H), 5.29 (s, 2 H), 5.61 (s, 2 H), 7.05-7.13 (m, 3 H), 7.42 (dd, J = 6.6, 14.3 Hz, 1H), 7.52 (d, J = 13.5 Hz, 2 H), 7.65-7.73 (m, 2 H), 8.08 (d, J = 13.6 Hz, 2 H).

5

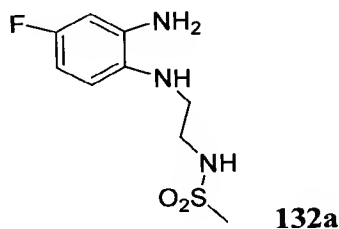
**131**

Compound **131** was prepared using the same procedure as compound **98** with compounds **121b** and **130b**:

10

^1H NMR ($\text{DMSO}-d_6$) δ 1.96-1.98 (m, 2 H), 3.21 (s, 3 H), 3.23 (s, 3 H), 3.35 (bs, 2 H), 4.33 (t, J = 6.2 Hz, 2 H), 5.25 (s, 2 H), 5.66 (s, 2 H), 7.01 (t, J = 8.9 Hz, 1 H), 7.20 (t, J = 4.2 Hz, 1 H), 7.37 (t, J = 7.7 Hz, 1 H), 7.45 (d, J = 8.4 Hz, 1 H), 7.55 (dd, J = 4.5, 8.4 Hz, 1 H), 7.75 (d, J = 7.7 Hz, 2 H), 7.83 (d, J = 6.9 Hz, 1 H), 7.98 (d, J = 7.9 Hz, 2 H).

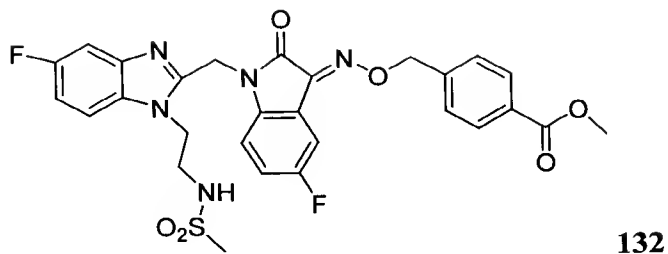
15

**132a**

Compound **132a** was prepared using the same procedure as compound **23e** starting with 2,5-difluoronitrobenzene and was used immediately upon isolation.

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143

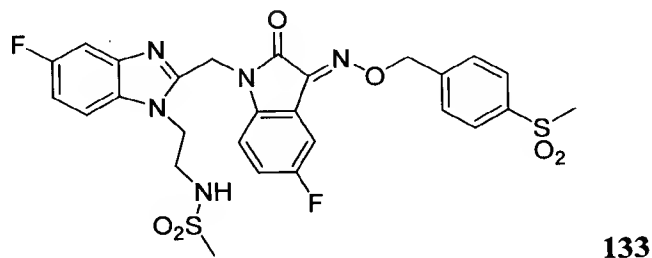


Compound **132** was prepared using the same procedure as compound **108** with compounds **118d** and **132a**:

5

^1H NMR (DMSO- d_6) δ 2.83 (s, 3 H), 3.41 (q, J = 5.9 Hz, 2 H), 3.86 (s, 3 H), 4.46 (t, J = 5.8 Hz, 2 H), 5.33 (s, 2 H), 5.64 (s, 2 H), 7.13-7.19 (m, 2 H), 7.33 (dt, J = 2.7, 9.1 Hz, 1 H), 7.34-7.44 (m, 2 H), 7.64 (d, J = 8.2 Hz, 3 H), 7.80 (dd, J = 2.7, 8.1 Hz, 1 H), 8.02 (d, J = 8.3 Hz, 2 H).

10



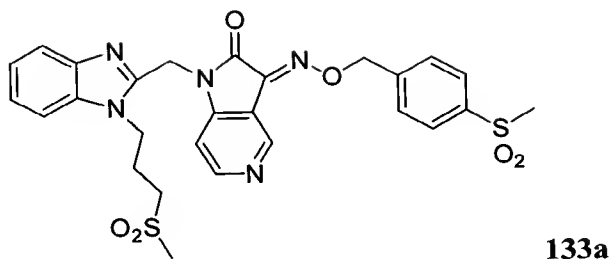
Compound **133** was prepared using the same procedure as compound **108** with compounds **121b** and **132a**:

15

^1H NMR (DMSO- d_6) δ 2.86 (s, 3 H), 3.24 (s, 3 H), 3.39-3.43 (m, 2 H), 4.48 (t, J = 5.7 Hz, 2 H), 5.36 (s, 2 H), 5.67 (s, 2 H), 7.17-7.20 (m, 2 H), 7.34 (dt, J = 2.5, 9.1 Hz, 1 H), 7.45-7.39 (m, 2 H), 7.68 (dd, J = 4.8, 9.0 Hz, 1 H), 7.76 (d, J = 8.4 Hz, 2 H), 7.85 (dd, J = 2.7, 8.1 Hz, 1 H), 7.99 (d, J = 8.4 Hz, 2 H).

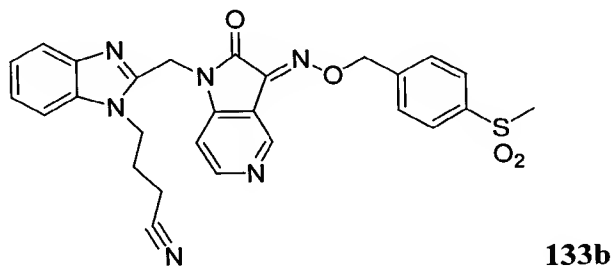
20

144



To a solution of 1H-pyrrolo[3,2-c]pyridine-2,3-dione (0.45 g, 3.1 mmol) [prepared as described in Rivalle, *J. Het. Chem.*, **1997**, 34, 491.] in MeOH (20 ml) was added p-toluenesulfonic acid (0.6 g, 3.1 mmol) and O-(4-methanesulfonyl-benzyl)-hydroxylamine (0.62 g, 3.1 mmol). The mixture was stirred areflux for 12h then cooled and filtered. The solid was the desired 1H-pyrrolo[3,2-c]pyridine-2,3-dione 3-[O-(4-methanesulfonyl-benzyl)-oxime which was used without further purification as described for the preparation of **134** using **10d** and the compound above with BTPP as base to give **133a**.

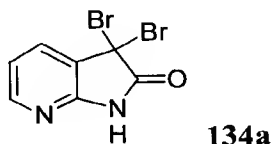
¹HNMR (DMSO) δ : 2.20-2.23 (m, 2 H), 3.00 (s, 3 H), 3.25-3.30 (m, 2 H), 4.45-4.48 (m, 2 H), 5.33 (s, 2 H), 5.70 (s, 2 H), 7.17 (t, $J = 7.5$ Hz, 1 H), 7.26 (t, $J = 7.7$ Hz, 1 H), 7.32 (d, $J = 5.25$ Hz, 1 H), 7.54 (d, $J = 8.0$ Hz, 1 H), 7.63 (d, $J = 8.1$ Hz, 1 H), 7.76 (d, $J = 8.3$ Hz, 2 H), 7.98 (d, 8.3 Hz, 2 H), 8.56 (d, $J = 5.4$ Hz, 1 H), 9.02 (s, 1 H); MS m/e 581 (MH^+).



20

Compound **133b** was prepared as described for **133a** using compound **25b** and BTPP as base.

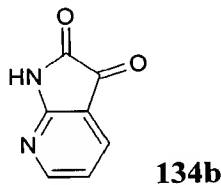
- ¹H NMR (DMSO) δ : 2.10-2.17 (m, 2 H), 2.60-2.65 (m, 2 H), 3.23 (s, 3 H), 4.35-4.42 (m, 2 H), 5.32 (s, 2 H), 5.70 (s, 2 H), 7.16 (t, $J = 7.3$ Hz, 1 H), 7.29 (t, $J = 7.3$ Hz, 1 H), 7.31 (d, $J = 6.5$ Hz, 1 H), 7.55 (d, $J = 8.1$ Hz, 1 H), 7.62 (d, $J = 8.1$ Hz, 1 H), 7.77 (d, $J = 8.3$ Hz, 2 H), 7.98 (d, $J = 8.3$ Hz, 2 H), 8.56 (d, $J = 6.5$ Hz, 1 H),
5 9.03 (s, 1 H);
MS m/e 528 (MH^+).



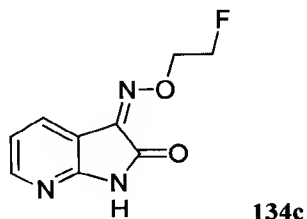
- 10 3,3-Dibromo 7-aza oxindole **134a** was prepared using a procedure described by Marfat, etc (*Tetrahedron Lett.*, **1987**, 28, 4027-4031) or using the procedure below.

- To a solution of 7-azaindole (2.0 g, 0.016 mol) in *tert.* BuOH (120 mL)
15 was added $PyBr_3$ in portions. The resulting mixture was stirred at room temperature for 15 hours. The solvent was removed *in vacuo* and the residue was suspended in water (250 mL). The aqueous phase was extracted with ethyl acetate (2 x 150 mL) and the combined organic fractions were washed with water (2 x 100 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$) and
20 evaporated. The residue was triturated in methylene chloride and filtered to afford 3.72 g of compound **134a** (80%) as a white-brown solid:

¹H NMR ($CDCl_3$) δ 8.25 (dd, $J = 1.4, 5.3$ Hz, 1H), 7.88 (dd, $J = 1.4, 7.6$ Hz, 1H), 7.16 (dd, $J = 5.3, 7.6$ Hz, 1H);
MS m/e 293 (MH^+).



Compound **134b** was prepared from the dibromide above according to the procedure described by J. Lloyd et al. (*Bioorganic and Medicinal Chemistry Letters*, **1994**, *4*, 195-200).



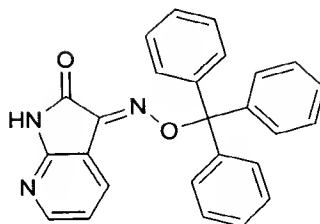
5

A solution of compound **134b** (300 mg, 1.03 mmol) in DMSO (25 mL) was heated at 95°C under house vacuum for 6.5 hours. The solution containing the corresponding 7-aza isatin was cooled to room temperature, followed by the addition O-(2-Fluoro-ethyl)-hydroxylamine hydrochloride (prepared as described by Ishikawa et al *J. Antibiot.*, **2000**, *53*, 1071) (131 mg, 1.13 mmol). After stirring for 1 hour at room temperature the mixture was quenched with water and extracted with ethyl acetate (6 x 25 mL). The combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed *in vacuo* and the residue purified by flash column chromatography (gradient, 2% MeOH in methylene chloride to 3%) to give compound **134c** (200 mg, 93%) as an orange solid that was further purified by trituration from diethyl ether-methylene chloride (1:1).

¹H NMR (DMSO) δ 11.5 (s, 1 H), 4.57-4.84 (m, 4 H), 7.08 (m, 1 H), 8.10 (d, J = 7.0 Hz, 1 H), 8.24 (d, J = 4.1 Hz, 1 H); MS m/e 210 (MH⁺).

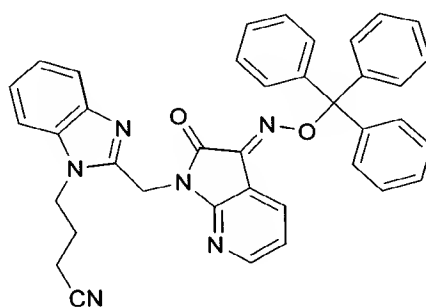
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**134d**

Compound **134b** (0.972 g, 6.56 mmol) was combined with *o*-tritylhydroxylamine (1.90 g, 6.56 mmol) in a mixture of EtOH (20 mL) and water (5 mL). The resulting mixture was briefly heated to boiling with a heat gun and then allowed to cool to room temperature. The suspension was chilled in an ice bath and filtered to isolate the crude pink solid which was rinsed with a mixture of cold 4:1 ethanol:water. The solid was dissolved with heating in chloroform and the resulting warm solution was passed through a plug of silica gel to remove the pink contaminant. Concentration *in vacuo* afforded 1.67 g (63% yield) of compound **134d** as a yellow powder:

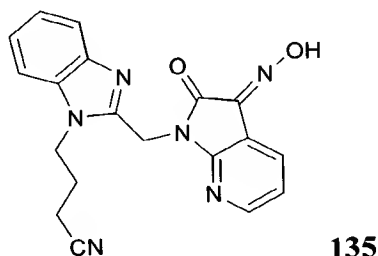
^1H NMR (DMSO- d_6) δ 7.15 (dd, $J = 7.4$ Hz, 5.3 Hz, 1 H), 7.27-7.28 (m, 6 H), 7.34-7.42 (m, 9 H), 8.24 (dd, $J = 7.5$ Hz, 1.4 Hz, 1 H), 8.27 (dd, $J = 5.3$ Hz, 1.5 Hz), 11.47 (s, 1 H);
MS m/e 428 ($M+\text{Na}^+$), 833 ($2M+\text{Na}^+$).

**134**

Compound **134d** (0.75 g, 1.85 mmol) was combined with cesium carbonate (1.81 g, 5.55 mmol) in DMF (20 mL), and the suspension was stirred at room temperature for 10 minutes. Compound **25b** (0.50 g, 1.85 mmol) was

added. The orange mixture was stirred at room temperature for 4.3 hours and the color of the reaction mixture became olive green all at once. The reaction mixture was diluted with ethyl acetate (100 mL) and water (100 mL). The phases were separated, and the organic layer was washed with water (2 x 50 mL) and brine (50 mL). The deep olive green mixture was dried over anhydrous MgSO_4 and it slowly became orange in color. The mixture was filtered and the filtrate concentrated *in vacuo*. The resulting crude solid was recrystallized from EtOAc to give 0.98 g (88% yield) of compound **134** as a yellow powder:

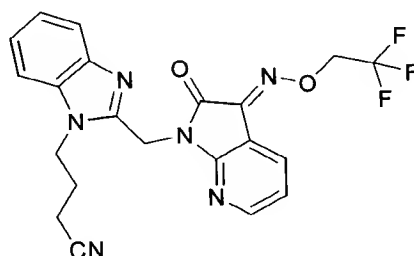
^1H NMR (DMSO-d_6) δ 2.13-2.16 (m, 2 H), 2.63 (t, $J = 7.4$ Hz, 2 H), 4.42 (t, $J = 7.4$ Hz, 2 H), 5.24 (s, 2 H), 7.13-7.16 (m, 1 H), 7.22-7.26 (m, 2 H), 7.31-7.32 (m, 6 H), 7.36-7.39 (m, 3 H), 7.41-7.44 (m, 6 H), 7.50 (d, $J = 8.0$ Hz, 1 H), 7.59 (d, $J = 8.1$ Hz, 1 H), 8.28 (dd, $J = 1.6, 5.4$ Hz, 1 H), 8.34 (dd, $J = 1.6, 7.5$ Hz, 1 H); MS m/e 603 (MH^+).



Compound **134** (0.50 g, 0.83 mmol) and *p*-toluenesulfonic acid monohydrate (0.141 g, 0.75 mmol) were combined in anhydrous CH_3CN (8 mL) in a sealed tube and the mixture was heated to 100 °C for 1 hour. Upon cooling, the product came out of solution as spherical crystals. The crystals were filtered from the mixture and rinsed with cold CH_3CN to give 0.39 g (86% yield) of compound **135** as a mono-*p*-toluenesulfonic acid salt:

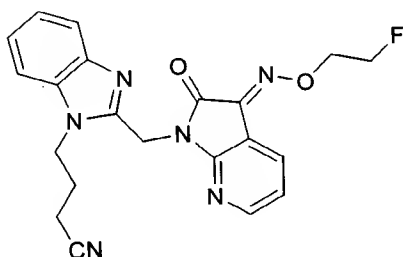
^1H NMR (DMSO-d_6) δ 2.26 (t, $J = 7.6$ Hz, 2 H), 2.29 (s, 3 H), 2.72 (t, $J = 7.5$ Hz, 2 H), 4.67 (t, $J = 7.4$ Hz, 2 H), 5.60 (s, 2 H), 7.11 (d, $J = 8.1$ Hz, 2 H), 7.19 (dd, $J = 5.4, 7.4$ Hz, 1 H), 7.47 (d, $J = 8.3$ Hz, 2 H), 7.56 (t, $J = 7.7$ Hz, 1 H), 7.62 (t, $J =$

7.7 Hz, 1 H), 7.73 (d, $J = 8.0$ Hz, 1 H), 8.04 (d, $J = 8.3$ Hz, 1 H), 8.22 (dd, $J = 1.6$, 5.3 Hz, 1 H), 8.30 (dd, $J = 1.6$, 7.5 Hz, 1 H), 13.99 (s, 1 H);
MS m/e 361 (MH^+).

**136**

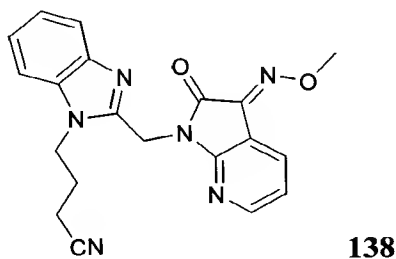
Compound **135** (68 mg, 0.12 mmol), 2,2,2-trifluoroethyl *p*-toluenesulfonate (0.035 g, 0.135 mmol) and BEMP on polystyrene (Fluka, 0.17 g, 0.37 mmol) were combined in anhydrous CH_3CN (3 mL) and the mixture was heated to 70 °C for 48 hours. Solids were removed from the mixture by filtration and rinsed with methanol. The filtrate was concentrated *in vacuo*, and the crude product was purified by preparative HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) to give 25 mg (36% yield) of a trifluoroacetic acid salt of compound **136** as a yellow glassy solid:

1H NMR ($DMSO-d_6$) δ 2.18-2.24 (m, 2 H), 2.68 (t, $J = 7.4$ Hz, 2 H), 4.53 (t, $J = 7.4$ Hz, 2 H), 5.24 (q, $J = 8.9$ Hz, 2 H), 5.42 (s, 2 H), 7.23 (dd, $J = 5.4$, 7.5 Hz, 1 H), 7.33 (t, $J = 7.5$ Hz, 1 H), 7.41 (t, $J = 7.4$ Hz, 1 H), 7.62 (d, $J = 8.0$ Hz, 1 H), 7.79 (d, $J = 8.0$ Hz, 1 H), 8.19 (dd, $J = 1.5$, 7.5 Hz, 1 H), 8.30 (dd, $J = 1.5$, 5.3 Hz, 1 H);
MS m/e 443 (MH^+).

**137**

Compound **137** was prepared using the same procedure as compound **136**. Excess electrophile was scavenged by the addition of PS-thiophenol resin (Argonaut, 100 mg), which was stirred with the reaction mixture for 4 hours. Purification by preparative HPLC (gradient, 10% MeOH in H₂O with 0.1% TFA to 90% MeOH in H₂O with 0.1% TFA) gave 15 mg (23 % yield) of a trifluoroacetic acid salt of compound **137** as a red glassy solid:

¹H NMR (DMSO-d₆) δ 2.18-2.24 (m, 2 H), 2.68 (t, J = 7.4 Hz, 2 H), 4.53 (t, J = 7.4 Hz, 2 H), 4.78-4.80 (m, 2 H), 4.81 (dt, J = 3.7, 81.8 Hz, 2 H), 5.42 (s, 2 H), 7.20 (dd, J = 5.3, 7.4 Hz, 1 H), 7.34 (t, J = 7.6 Hz, 1 H), 7.41 (t, J = 7.6 Hz, 1 H), 7.60 (d, J = 8.1 Hz, 1 H), 7.78 (d, J = 7.7 Hz, 1 H), 8.24-8.27 (m, 2 H); MS m/e 407 (MH⁺).



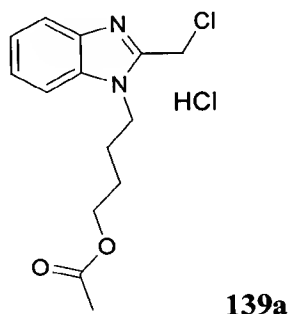
15

A mixture of compound **135** (68 mg, 0.12 mmol), cesium carbonate (0.12 g, 0.37 mmol) and iodomethane (19 mg, 0.14 mmol) in anhydrous CH₃CN (3 mL) was stirred for 18 hours at room temperature. The mixture became a deep olive green color during the course of the reaction. Excess iodomethane was scavenged by the addition of PS-thiophenol resin (Argonaut, 100 mg), which was stirred with the reaction mixture for 2 hours. Solids were removed by filtration and rinsed with MeOH. The filtrate was concentrated *in vacuo* to a green solid. The crude product was purified by preparative HPLC (gradient, 10% MeOH in H₂O with 0.1% TFA to 90% MeOH in H₂O with 0.1% TFA) to give 12 mg (20% yield) of a trifluoroacetic acid salt of compound **138** as a red glassy solid:

25

^1H NMR (DMSO- d_6) δ 2.17-2.23 (m, 2 H), 2.68 (t, J = 7.4 Hz, 2 H), 4.29 (s, 3 H), 4.53 (t, J = 7.4 Hz, 2 H), 5.42 (s, 2 H), 7.17 (dd, J = 5.3, 7.4 Hz, 1 H), 7.32 (t, J = 7.5 Hz, 1 H), 7.40 (t, J = 7.5 Hz, 1 H), 7.60 (d, J = 8.0 Hz, 1 H), 7.78 (d, J = 8.0 Hz, 1 H), 8.21 (dd, J = 1.5, 7.4 Hz, 1 H), 8.25 (dd, J = 1.5, 5.3 Hz, 1 H);

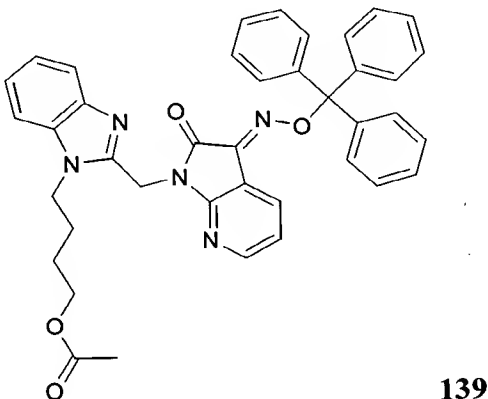
5 MS m/e 375 (MH^+).



Compound **139a** was prepared using the same procedure as compound
 10 **25b** with 4-bromobutyl acetate:

^1H NMR (CDCl_3) δ 1.80-1.86 (m, 2 H), 2.03 (s, 3 H), 2.06-2.12 (m, 2 H), 4.14 (t, J = 6.1 Hz, 2 H), 4.55 (t, J = 8.1 Hz, 2 H), 5.42 (s, 2 H), 7.48 (t, J = 7.3 Hz, 1 H), 7.55 (t, J = 7.3 Hz, 1 H), 7.64 (d, J = 8.5 Hz, 1 H), 7.78 (d, J = 8.2 Hz, 1 H);

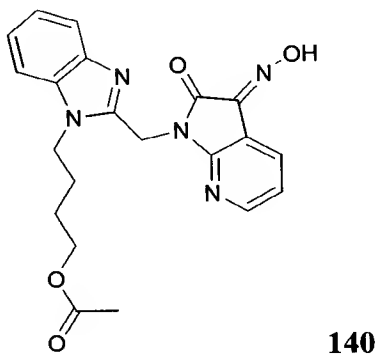
15 MS m/e 281 (MH^+).



A mixture of compound **134b** (0.75 g, 1.85 mmol) and cesium carbonate (1.81 g, 5.55 mmol) in DMF (20 mL) was stirred at room temperature for 10

minutes. After addition of compound **139a** (0.59 g, 1.85 mmol), the orange mixture was stirred at room temperature for 2.5 hours and the reaction mixture became olive green in color. The reaction mixture was diluted with EtOAc (100 mL) and water (100 mL). The phases were separated and the organic layer was washed with water (2 x 50 mL) and brine (50 mL). The deep olive green organic layer was dried over anhydrous MgSO_4 and it slowly became orange in color. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by flash chromatography ($\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}$, 50:1) and then recrystallized from EtOAc to give 0.73 g (61% yield) of compound **139** as a yellow powder:

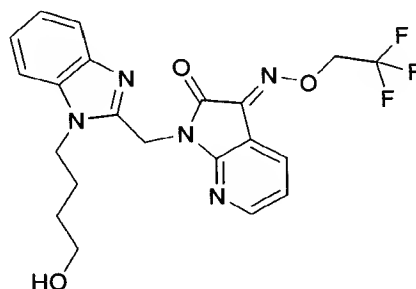
^1H NMR ($\text{DMSO}-d_6$) δ 1.63-1.67 (m, 2 H), 1.82-1.85 (m, 2 H), 4.03 (t, $J = 6.5$ Hz, 2 H), 4.38 (t, $J = 7.3$ Hz, 2 H), 5.22 (s, 2 H), 7.11-7.14 (m, 1 H), 7.20-7.26 (m, 2 H), 7.31-7.32 (m, 6 H), 7.36-7.39 (m, 3 H), 7.41-7.44 (m, 6 H), 7.49 (d, $J = 8.0$ Hz, 1 H), 7.58 (d, $J = 8.1$ Hz, 1 H), 8.28 (dd, $J = 1.6, 5.4$ Hz, 1 H), 8.35 (dd, $J = 1.6, 7.5$ Hz, 1 H);
MS m/e 650 (MH^+).



Compound **140** was prepared using the same procedure as compound **135**. Purification by flash chromatography (gradient, $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}$, 30:1 to 10:1) gave 0.15 g (70% yield) of compound **140** as a yellow glassy solid:

^1H NMR ($\text{DMSO}-d_6$) δ 1.66-1.69 (m, 2 H), 1.84-1.87 (m, 2 H), 1.99 (s, 3 H), 4.05 (t, $J = 6.5$ Hz, 2 H), 4.40 (t, $J = 7.4$ Hz, 2 H), 5.27 (s, 2 H), 7.12-7.15 (m, 2 H),

7.22 (t, $J = 8.1$ Hz, 1 H), 7.48 (d, $J = 8.0$ Hz, 1 H), 7.59 (d, $J = 8.1$ Hz, 1 H), 8.21 (dd, $J = 1.6, 5.3$ Hz, 1 H), 8.27 (dd, $J = 1.6, 7.4$ Hz, 1 H), 13.89 (s, 1 H);
MS m/e 408 (MH^+).

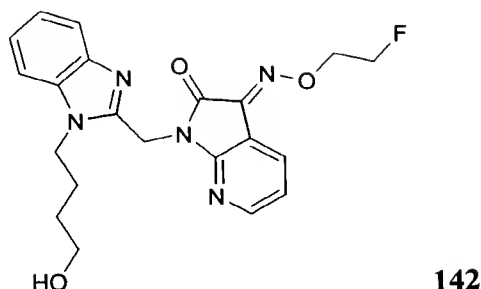
**141**

A mixture of compound **140** (0.05 g, 0.12 mmol), 2,2,2-trifluoroethyl *p*-toluenesulfonate (0.035 g, 0.14 mmol) and BEMP on polystyrene (Fluka, 0.17 g, 0.37 mmol) in anhydrous CH_3CN (3 mL) was heated to 70 °C for 18 hours.

MeOH (1 mL) was added to remove the acetate group and the mixture was heated to 70 °C for 4 hours. Solids were removed by filtration and rinsed with methanol. The filtrate was concentrated *in vacuo*, and the crude product was purified by preparative HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) to give 0.025 g (37% yield) of a trifluoroacetic acid salt of compound **141** as an off-white powder:

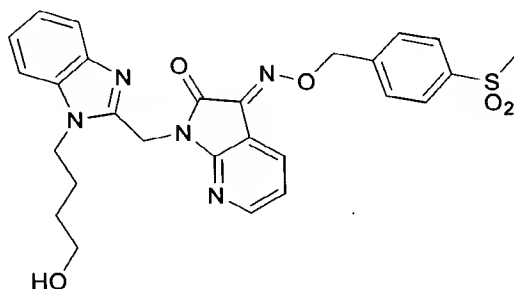
1H NMR ($DMSO-d_6$) δ 1.50-1.56 (m, 2 H), 1.85-1.91 (m, 2 H), 3.42-3.49 (m, 2 H), 4.50 (t, $J = 7.4$ Hz, 2 H), 5.24 (q, $J = 9.0$ Hz, 2 H), 5.43 (s, 2 H), 7.23-7.27 (m, 1 H), 7.36-7.38 (m, 1 H), 7.42-7.45 (m, 1 H), 7.63 (d, $J = 8.1$ Hz, 1 H), 7.81 (d, $J = 7.9$ Hz, 1 H), 8.17-8.21 (m, 1 H), 8.28-8.32 (m, 1 H);
MS m/e 448 (MH^+).

154

**142**

Compound **142** was prepared using the same procedure as compound **141**. Excess electrophile was scavenged by the addition of PS-thiophenol resin (Argonaut, 100 mg), which was stirred with the reaction mixture for 4 hours. Purification by preparative HPLC (gradient, 10% MeOH in H₂O with 0.1% TFA to 90% MeOH in H₂O with 0.1% TFA) gave 0.012 g (19 % yield) of a trifluoroacetic acid salt of compound **142** as an off-white solid:

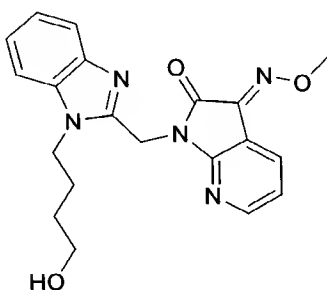
¹H NMR (DMSO-d₆) δ 1.51-1.56 (m, 2 H), 1.85-1.91 (m, 2 H), 3.45 (t, J = 6.3 Hz, 2 H), 4.50 (t, J = 7.4 Hz, 2 H), 4.74-4.83 (m, 2 H), 4.81 (dt, J = 2.6, 83.1 Hz, 2 H), 7.20-7.22 (m, 1 H), 7.36-7.37 (m, 1 H), 7.41-7.44 (m, 1 H), 7.63 (d, J = 8.0 Hz, 1 H), 7.81 (d, J = 7.9 Hz, 1 H), 8.24-8.27 (m, 2 H); MS m/e 412 (MH⁺).

**143**

Compound **143** was prepared by the same procedure as described for the preparation of compound **141**. Excess electrophile was scavenged by the addition of PS-thiophenol resin (Argonaut, 100 mg), which was stirred with the reaction mixture for 4 hours. Purification by preparative HPLC (gradient, 10% MeOH in H₂O with 0.1% TFA to 90% MeOH in H₂O with 0.1% TFA) gave a mixture of

compound **143** plus the trifluoroacetate ester of compound **143**. This mixture was dissolved in methanol and the resulting solution was treated with MP-carbonate resin (Argonaut) for 18 hours at room temperature. Filtration to remove the resin followed by concentration of the filtrate *in vacuo* gave 0.022 g (34 % yield) of
5 compound **143** as a yellow glassy solid:

^1H NMR (DMSO- d_6) δ 1.48-1.51 (m, 2 H), 1.81-1.84 (m, 2 H), 3.24 (s, 3 H),
3.43-3.45 (m, 2 H), 4.36 (t, $J = 7.3$ Hz, 2 H), 4.50 (t, $J = 5.1$ Hz, 1 H), 5.25 (s, 2
H), 5.68 (s, 2 H), 7.12 (t, $J = 8.0$ Hz, 1 H), 7.17-7.22 (m, 2 H), 7.47 (d, $J = 8.0$ Hz,
10 1 H), 7.56 (d, $J = 8.1$ Hz, 1 H), 7.76 (d, $J = 8.3$ Hz, 2 H), 7.99 (d, $J = 8.3$ Hz, 2 H),
8.26-8.28 (m, 2 H);
MS m/e 534 (MH^+).

**144**

15

A mixture of compound **140** (0.050 g, 0.12 mmol) with cesium carbonate (0.12 g, 0.37 mmol) and iodomethane (0.019 g, 0.14 mmol) in anhydrous CH_3CN (3 mL) was stirred for 18 hours at room temperature. The mixture became a deep olive green color during the course of the reaction. MeOH (1 mL) was added to
20 remove the acetate group, and excess iodomethane was scavenged by the addition of PS-thiophenol resin (Argonaut, 100 mg) which was stirred with the reaction mixture for 2 hours. Solids were removed by filtration and rinsed with MeOH and the filtrate was concentrated *in vacuo* to a green solid. Purification of the crude product by preparative HPLC (gradient, 10% MeOH in H_2O with 0.1%
25 TFA to 90% MeOH in H_2O with 0.1% TFA) gave a mixture of compound **144** plus the trifluoroacetate ester of compound **144**. This mixture was dissolved in MeOH and the resulting solution was treated with MP-carbonate resin (Argonaut)

for 18 hours at room temperature. Filtration to remove the resin followed by concentration of the filtrate *in vacuo* gave 0.007 g (16% yield) of compound **144** as a yellow glassy solid:

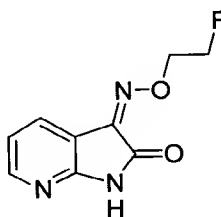
- 5 ^1H NMR (DMSO- d_6) δ 1.49-1.52 (m, 2H), 1.81-1.84 (m, 2H), 3.43-3.46 (m, 2H), 4.28 (s, 3H), 4.37 (t, J = 7.4 Hz, 2H), 4.51 (t, J = 5.1 Hz, 1H), 5.27 (s, 2H), 7.11-7.17 (m, 2H), 7.20-7.23 (m, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 8.20 (dd, J = 1.6, 7.4 Hz, 1H), 8.25 (dd, J = 1.6, 5.3 Hz, 1H); MS m/e 380 (MH^+).

10

O-(2-Fluoro-ethyl)-hydroxylamine was prepared using a procedure described by Ishikawa, et al *J. Antibiot.*, **2000**, 53, 1071.

15

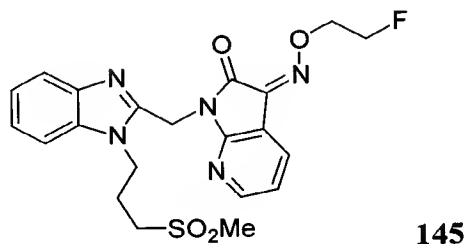
1H-Pyrrolo[2,3-b]pyridine-2,3-dione 3-[O-(2-fluoro-ethyl)-oxime]



- A solution of compound **134a** (300 mg, 1.03 mmol) in DMSO (25 mL) was heated at 95 $^{\circ}\text{C}$ at 15 torr for 6.5 hours: The solution containing the corresponding 7-aza isatin was cooled to room temperature, followed by the addition O-(2-Fluoro-ethyl)-hydroxylamine hydrochloride (131 mg, 1.13 mmol). After stirring for 1 hour at room temperature the mixture was quenched with water and extracted with ethyl acetate (6 x 25 mL). The combined organic phases were washed with brine and dried over MgSO_4 . The solvent was removed *in vacuo* and the residue purified by flash column chromatography (gradient, 2% MeOH in methylene chloride to 3%) to give 1H-Pyrrolo[2,3-b]pyridine-2,3-dione 3-[O-(2-fluoro-ethyl)-oxime] (200 mg, 93%) as an orange solid that was further purified by trituration from diethyl ether-methylene chloride (1:1).

^1H NMR (CDCl_3) δ do 3.48 (s, 3 H), 4.97 (s, 2 H), 7.40-7.50 (m, 2 H), 7.75-7.85 (m, 2 H);

MS m/e 209 (MH^+).



5

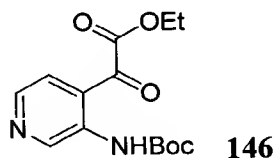
Compound **145** was prepared according the procedure for the preparation of compound **134**, starting from 1H-pyrrolo[2,3-b]pyridine-2,3-dione 3-[O-(2-fluoro-ethyl)-oxime] (18.9 mg, 0.0904 mmol) and **10d** (29.2 mg, 0.0904 mmol).

10 Purification was accomplished by trituration from methylene chloride-methanol to give compound **145** (18 mg, 43% yield) as a yellow solid.

^1H NMR (DMSO) δ 8.26 (dd, $J = 1.6, 5.3$ Hz, 1H), 8.23 (dd, $J = 1.6, 7.5$ Hz, 1H), 7.63 (d, $J = 8.1$ Hz, 1H), 7.50 (d, $J = 8.0$ Hz, 1H), 7.25 (t, $J = 7.8$ Hz, 1H), 7.18 (dd, $J = 7.5, 5.3$ Hz, 1H), 7.14 (t, $J = 7.9$ Hz, 1 H), 5.30 (s, 2 H), 4.72-4.90 (m,

15 4H), 4.52 (t, $J = 7.4$ Hz, 2H), 3.30 (t, $J = 7.5$ Hz, 2H), 3.02 (s, 3H), 2.28 (m, 2H); MS m/e 460 (MH^+).

(3-tert-Butoxycarbonylamino-pyridin-4-yl)-oxo-acetic acid ethyl ester



20

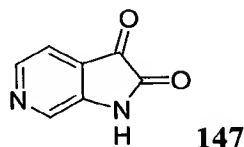
(3-tert-Butoxycarbonylamino-pyridin-4-yl)-oxo-acetic acid ethyl ester was prepared according to a procedure described by Estel, etc (*J. Heterocycl. Chem.*, **1989**, 26, 105-): To a solution of pyridin-3-yl-carbamic acid tert-butyl ester

25 (8.50 g, 43.8 mmol) and TMEDA (16.5 mL, 109 mmol) in THF (200 mL) at -78°C was cannulated *tert.*-BuLi (64.1 mL, 1.7 M in pentane) over 30 min under

nitrogen. The mixture was then stirred for 2 hours between -10°C and -20°C . After cooling to -60°C diethyl oxalate (17.8 mL, 131 mmol) was added and the mixture allowed to warm to 0°C . After 3 hours the mixture was poured onto ice/1M HCl (120 mL) and extracted with ethyl acetate (3x150 mL). The combined organic extracts were washed with water (100 mL), brine (75 mL), dried over MgSO_4 and concentrated. The residue was purified by flash column chromatography (gradient, hexane/ethyl acetate 5:2, 2:1), to give 3.04 g (24% yield) of compound **146** as a yellow oil.

^1H NMR (DMSO) δ 9.80 (s, 1H), 9.70 (br s, 1H), 8.40 (d, J 5.2 Hz, 1H), 7.50 (d, J = 5.2 Hz, 1H), 4.44 (q, J = 7.2 Hz, 2H), 1.41 (t, J = 7.2 Hz, 3H); MS m/e 327 ($\text{M}^+ - \text{MeOH}^+$).

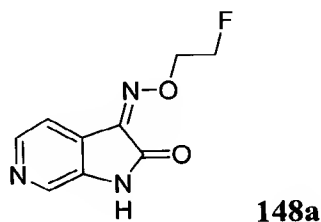
1H-Pyrrolo[2,3-c]pyridine-2,3-dione



Compound **146** (1.62 g, 5.50 mmol) was heated for 7 min at $180\text{--}190^{\circ}\text{C}$ in a kugelrohr oven at 15 torr. The remaining black solid **147** (823 mg) was used without further purification.

^1H NMR (DMSO) δ 11.2 (s, 1H), 8.45 (br s, 1H), 8.34 (br s, 1H), 7.41 (br s, 1H); MS m/e 180 ($\text{M}^+ - \text{MeOH}^+$).

1H-Pyrrolo[2,3-c]pyridine-2,3-dione 3-[O-(2-fluoro-ethyl)-oxime]

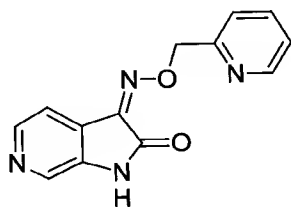


1H-Pyrrolo[2,3-c]pyridine-2,3-dione (208 mg, 1.40 mmol) was dissolved in DMSO (5 mL) and treated with O-(2-Fluoro-ethyl)-hydroxylamine (243 mg, 2.11 mmol). After stirring for 1 hour at room temperature, water (30 mL) was added and the mixture extracted with ethyl acetate (6x20 mL). The combined organic
5 extracts were washed with brine, dried over MgSO₄ and concentrated. The residue was triturated from diethyl ether to give 130 mg (44% yield over 2 steps) of **148a** as a yellow solid.

¹H NMR (DMSO) δ 11.0 (s, 1H), 8.40 (d, J = 4.8 Hz, 1H), 8.28 (s, 1H), 7.73 (d, J = 4.7 Hz, 1H), 4.69 – 4.87 (m, 4H);

10 MS m/e 210 (MH⁺).

1H-Pyrrolo[2,3-c]pyridine-2,3-dione 3-(O-pyridin-2-ylmethyl-oxime)

**148b**

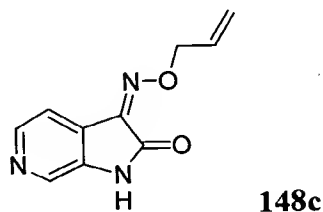
15

1H-Pyrrolo[2,3-c]pyridine-2,3-dione (110 mg, 0.743 mmol) was dissolved in DMSO (4 mL) and treated with O-pyridin-2-ylmethyl-hydroxylamine (176 mg, 0.892 mmol). After stirring for 1 hour at room temperature, DIPEA (129 μL, 0.743 mmol) was added and the mixture heated to 60°C and stirred for 2 hours at
20 the same temperature. The mixture was cooled to room temperature, water (20 mL) was added and the mixture extracted with ethyl acetate (7x15 mL). The combined organic extracts were washed with brine, dried over MgSO₄ and concentrated. The residue was purified by flash column chromatography (6% methanol in methylene chloride), to give 45 mg (24% yield over 2 steps) of
25 **148b** as a yellow solid.

¹H NMR (CDCl₃) δ 9.98 (s, 1H), 8.63 (d, J = 4.6 Hz, 1H), 8.42 (d, J = 4.8 Hz, 1H), 8.38 (s, 1H), 7.77 (d, J = 4.6 Hz, 1H), 7.73 (t, J = 7.7 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.28 (dd, J = 4.8, 7.4 Hz, 1H);

MS m/e 255 (MH⁺);

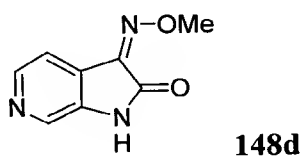
1H-Pyrrolo[2,3-c]pyridine-2,3-dione 3-(O-allyl-oxime)



5 Compound **147** (121 mg, 0.817 mmol) was dissolved in a mixture of MeCN (4 mL) and water (2 mL), and treated with O-Allyl-hydroxylamine (99 mg, 0.90 mmol). After stirring for 75 min at room temperature, another 50 mg of the O-Allyl-hydroxylamine was added. After 30 min. MeCN was stripped off and the residue extracted with ethyl acetate (7x15 mL). The combined organic extracts
10 were washed with brine, dried over MgSO₄ and concentrated. The resulting yellow solid **148c** (80 mg, 48% over two steps) was sufficiently pure for the next step.

¹H NMR (DMSO) δ 11.0 (s, 1H), 8.39 (d, J = 4.8 Hz, 1H), 8.27 (s, 1H), 7.70 (d, J = 4.8 Hz, 1H), 6.10 (m, 1H), 5.43 (d, J = 17.3 Hz, 1H), 5.34 (d, J = 10.5 Hz, 1H),
15 5.00 (d, J = 5.8 Hz, 1H).

1H-Pyrrolo[2,3-c]pyridine-2,3-dione 3-(O-methyl-oxime)

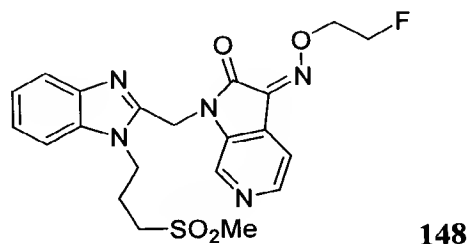


20 Compound **147** (154 mg, 1.04 mmol) was dissolved in a mixture of MeCN (4 mL) and water (2 mL), and treated with O-methyl-hydroxylamine (96 mg, 1.1 mmol). After stirring for 75 min at room temperature, another 48 mg of the O-methyl-hydroxylamine was added. After 30 min. the solvents were evaporated
25 and the residue purified by flash column chromatography (gradient, 5, 6, 7%

methanol in methylene chloride), to give 52 mg (28% yield over 2 steps) **148d** as a yellow solid.

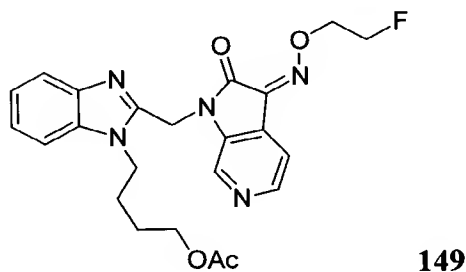
^1H NMR (DMSO) δ 11.0 (s, 3H), 8.37 (d, J = 4.7 Hz, 1H), 8.27 (s, 1H), 7.70 (d, J = 4.8 Hz, 1H), 4.26 (s, 3H);

5



Compound **148** was prepared according the procedure for the preparation of compound **134**, starting from isatin **148a** (19.9 mg, 0.0952 mmol) and **10d** (30.8 mg, 0.0952 mmol). Purification was accomplished by preparative TLC (eluens 5% methanol in methylene chloride) to give compound **148** (25 mg, 57% yield) as a yellow solid.

^1H NMR (DMSO) δ 8.26 (dd, J = 1.6, 5.3 Hz, 1H), 8.23 (dd, J = 1.6, 7.5 Hz, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.25 (t, J = 7.8 Hz, 1H), 7.18 (dd, J = 7.5, 5.3 Hz, 1H), 7.14 (t, J = 7.9 Hz, 1H), 5.30 (s, 2H), 4.72-4.90 (m, 4H), 4.52 (t, J = 7.4 Hz, 2H), 3.30 (t, J = 7.5 Hz, 2H), 3.02 (s, 3H), 2.28 (m, 2H); MS m/e 460 (MH^+);

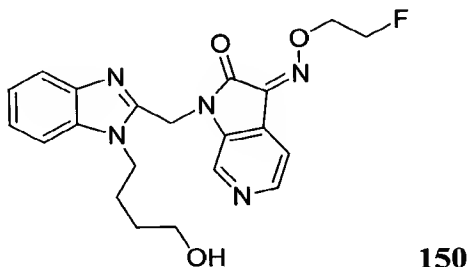


20

Compound **149** was prepared according the procedure for the preparation of compound **134**, starting from isatin **148a** (28.6 mg, 0.137 mmol) and **139a** (43.4 mg, 0.137 mmol). The product **149** was used as it is.

^1H NMR (CDCl_3) δ 8.90 (s, 1H), 8.49 (d, J = 4.8 Hz, 1H), 7.76 (m, 2H), 7.30 (m, 2H), 5.30 (s, 2H), 4.75 - 4.85 (m, 4H), 4.30 (t, J = 7.2 Hz, 2H), 4.05 (t, J = 6.3 Hz, 2H), 1.98 (s, 3H), 1.76 (m, 4H);
MS m/e 453 (MH^+).

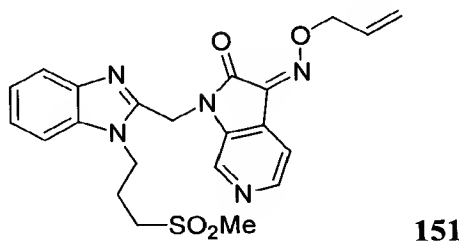
5



Compound **149** (0.137 mmol, assuming quantitative recovery) was dissolved in methanol (3 mL) and 5 drops of thionyl chloride were added. The solution was stirred overnight and the volatiles evaporated. The residue was redissolved in methanol and concentrated. This procedure was repeated three times. Purification was accomplished by preparative TLC (eluant 5% methanol in methylene chloride) to give compound **150** (27 mg, 48% yield over two steps) as a yellow solid.

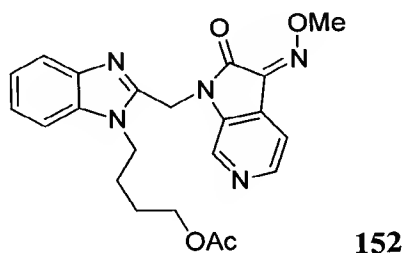
^1H NMR (DMSO) δ 8.57 (s, 1H), 8.49 (d, J = 4.8 Hz, 1H), 7.83 (d, J = 4.8 Hz, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.24 (t, J = 7.4 Hz, 1H), 7.17 (t, J = 7.3 Hz, 1H), 5.35 (s, 2H), 4.76 - 4.90 (m, 4H), 4.48 (t, J = 5.2 Hz, 1H), 4.34 (t, J = 7.4 Hz, 2H), 3.43 (q, J = 6.3 Hz, 2H), 1.77 (m, 2H), 1.49 (m, 2H);
MS m/e 412 (MH^+).

20

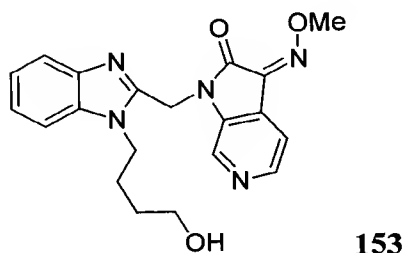


Compound **151** was prepared according the procedure for the preparation of compound **134**, starting from isatin **148c** (84 mg, 0.41 mmol) and **10d** (134 mg, 0.41 mmol). Purification was accomplished by flash column chromatography (eluent 5% methanol in methylene chloride), to give 118 mg (63% yield) of compound **151** as a yellow solid.

¹H NMR (DMSO) δ 8.61 (s, 1H), 8.48 (d, J = 4.8 Hz, 1H), 7.80 (d, J = 4.8 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.56 (d, J 8.0 Hz, 1 H), 7.28 (t, J 8.0 Hz, 1 H), 7.17 (t, J 8.0 Hz, 1H), 6.13 (m, 2H), 5.46 (d, J = 17.3 Hz, 1H), 5.36 (d, J = 10.5 Hz, 1H), 5.37 (s, 2H), 5.06 (d, J = 5.8 Hz, 2 H), 4.48 (t, J 7.5 Hz, 2H), 3.26 (t, J = 7.6 Hz, 2H), 3.02 (s, 3H), 2.22 (m, 2H);
MS m/e 454 (MH⁺);



Compound **152** was prepared according the procedure for the preparation of compound **134**, starting from isatin **148d** (14.3 mg, 0.0807 mmol) and **139a** (25.6 mg, 0.0807 mmol). The product was used as it is.
MS m/e 422 (MH⁺).



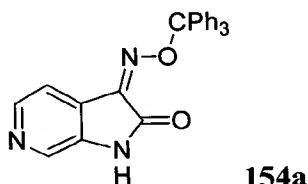
Compound **153**(0.0807 mmol, assuming quantitative recovery) was dissolved in methanol (2 mL) and acetyl chloride (58 μ L) was added. The

solution was stirred for 5 hours and the volatiles evaporated. The residue was redissolved in methanol and concentrated. This procedure was repeated three times. Purification was accomplished by flash column chromatography (eluent 6% methanol in methylene chloride), to give 9 mg (29% yield) of compound **153** as a yellow solid, which was converted into the HCl salt by dissolution in methanol and addition of 4N HCl in dioxane (6 μ L), followed by concentration.

^1H NMR (CDCl_3) δ 8.95 (s, 1H), 8.49 (d, $J = 4.8$ Hz, 1H), 7.77 (m, 1H), 7.23 (d, $J = 4.5$ Hz, 1H), 7.33 (m, 3H), 5.35 (s, 2H), 4.39 (s, 3H), 4.33 (m, 2H) 3.69 (t, $J = 6.1$ Hz, 2H), 1.82 (m, 2H), 1.67 (m, 2H);

MS m/e 380 (MH^+).

1H-Pyrrolo[2,3-c]pyridine-2,3-dione 3-(O-trityl-oxime)

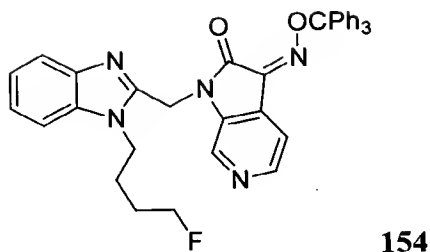


1H-Pyrrolo[2,3-c]pyridine-2,3-dione (298 mg, 2.01 mmol) was dissolved in DMSO (4 mL) and treated with O-Trityl-hydroxylamine (609 mg, 2.21 mmol). After stirring for 20 min. at room temperature, the temperature was raised to 70 $^{\circ}$ C and 30 min. later to 100 $^{\circ}$ C, and stirring was continued for 2 hours. After cooling to room temperature, water (30 mL) was added and the mixture extracted with ethyl acetate (2x50 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried over MgSO_4 and concentrated. Purification was accomplished by flash column chromatography (eluent 5% methanol in methylene chloride), to give 130 mg (13% yield) **154a** as a yellow oil.

^1H NMR (CDCl_3) δ 9.57 (br s, 1H), 8.47 (d, $J = 4.8$ Hz, 1H), 8.31 (s, 1H), 7.94 (d, $J = 4.8$ Hz, 1H), 7.32 (m, 15H);

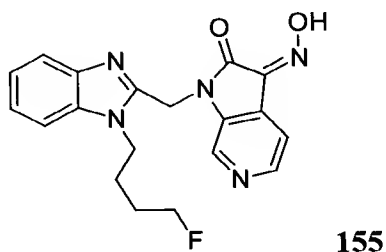
MS m/e 406 (MH^+).

165



Compound **154** was prepared according the procedure for the preparation of compound **134**, starting from **154a** (121 mg, 0.298 mmol) and **132c** (83 mg, 0.298 mmol). The residue after work-up was precipitated from diethyl ether to give **154** (114 mg) as a yellow solid. The rest was purified by flash column chromatography (eluent 3%, 5% methanol in methylene chloride), to give 13 mg of **154** for a combined yield of 127 mg (70%).

¹H NMR (CDCl₃) δ 8.94 (s, 1H), 8.52 (d, J = 4.7 Hz, 1 H), 8.93 (d, J = 4.7 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.35 (m, 18H), 5.31 (s, 2H), 4.25 – 4.28 (m, 4H), 1.69 (m, 4H).

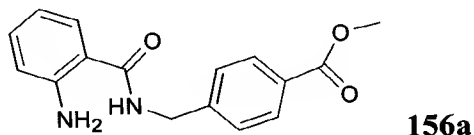


15

To a solution of **154** (127 mg, 0.208 mmol) in acetonitrile (3 mL) and methylene chloride (1 mL) was added *p*-TsOH.H₂O (59 mg, 0.312 mmol). The mixture was heated in a sealed tube at 100°C for 10 min. The solvents were removed *in vacuo* and the residue purified by flash column chromatography (eluent 3%, 5%, 8%, 10%, 15% methanol in methylene chloride), to give 58 mg (68%) of **155**, that was converted into the HCl salt by dissolving in methanol and addition of excess acetyl chloride. The product was a single configurational isomer in DMSO-d₆ (*Z*-isomer), but was a 5:1 mixture in methanol (CD₃OD).

^1H NMR (CD_3OD) δ 8.97 (s, 1H), 8.76 (d, $J = 5.7$ Hz, 1 H), 8.62 (d, $J = 5.7$ Hz, 1H), 8.00 (d, $J = 8.2$ Hz, 1H), 7.75 (d, $J = 8.2$ Hz, 1H), 7.69 (t, $J = 7.3$ Hz, 1H), 7.64 (t, $J = 7.3$ Hz, 1H), 5.86 (s, 2H), 4.71 (t, $J = 7.9$ Hz, 2H), 4.57 (dt, $J = 5.8, 4.7$ Hz, 2H), 2.18 (m, 2H), 1.94 (m, 2H);

5 MS m/e 368 (MH^+).



10 A solution of anthranilic acid (1.66 g, 12.10 mmol), hydroxybenztriazole (1.64 g, 12.10 mmol), and methyl 4-(methylamino)benzoate (2.0 g, 12.10 mmol) in DMF (20 mL) was treated with EDAC (2.32 g, 12.10 mmol) and the mixture was stirred at room temperature for 12 hours. The solvent was removed and the residue was dissolved in EtOAc, washed with 1N HCl, saturated aqueous NaHCO_3 , dried over MgSO_4 and concentrated. The residue was purified by flash
15 chromatography (hexanes:EtOAc = 5:1) to give 2.05 g (59% yield) of compound **156a** as a white solid:

^1H NMR ($\text{DMSO}-d_6$) δ 3.82 (s, 3 H), 4.49 (d, $J = 5.9$ Hz, 2 H), 4.58 (d, $J = 5.9$ Hz, 2 H), 6.44-6.59 (m, 3 H), 6.70 (d, $J = 8.2$ Hz, 1H), 6.78 (d, $J = 8.2$ Hz, 1 H),
20 7.13-7.22 (m, 2 H), 7.44 (d, $J = 8.2$ Hz, 2 H), 7.48 (d, $J = 8.2$ Hz, 2 H), 7.57 (d, $J = 6.9$ Hz, 2 H), 7.88-7.94 (m, 2 H), 8.55 (d, $J = 8.3$ Hz, 1 H), 8.86 (t, $J = 5.9$ Hz, 1 H), 9.46 (t, $J = 5.9$ Hz, 1 H);

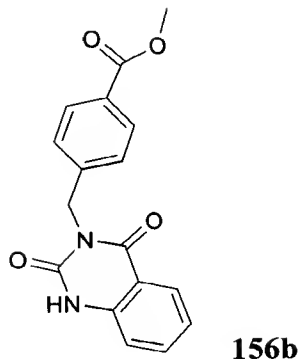
IR (KBr, cm^{-1}) 1706, 1654, 1528;

MS m/e 284 (MH^+);

25 Anal. Calcd for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_3$: C, 67.59; H, 5.67; N, 9.85

Found: C, 67.87; H, 5.63; N, 9.87.

167



To a mixture of compound **156a** (2.0 g, 7.04 mmol) and KHCO_3 (1.74 g, 17.30 mmol) in H_2O (50 mL) was added methyl chloroformate (1.09 mL, 14.00 mmol) and the mixture was stirred for 12 hours at room temperature. The resulting solid was isolated by filtration to give 2.4 g (99% yield) of the intermediate as a white solid. The solid was dissolved in MeOH (100 mL), treated with sodium methoxide (0.5 M, 1.0 mL) and heated to reflux for 4 hours. The precipitated product was isolated by filtration to give 1.58 g (73% yield) of compound **156b** as a white solid:

^1H NMR ($\text{DMSO}-d_6$) δ 3.83 (s, 3 H), 5.16 (s, 2 H), 7.23 (t, $J = 6.9$ Hz, 1 H), 7.43 (d, $J = 8.4$ Hz, 1 H), 7.72 (t, $J = 7.5$ Hz, 1 H), 7.69-7.96 (m, 4 H);

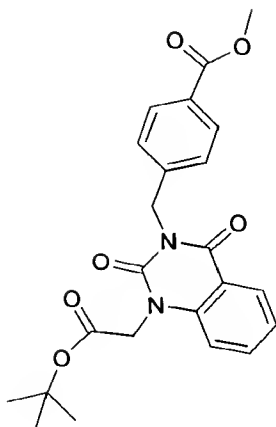
IR (KBr, cm^{-1}) 1718, 1656;

MS m/e 310 (MH^+);

Anal. Calcd for $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_4$: C, 65.80; H, 4.55; N, 9.03

Found: C, 65.77; H, 4.81; N, 8.83.

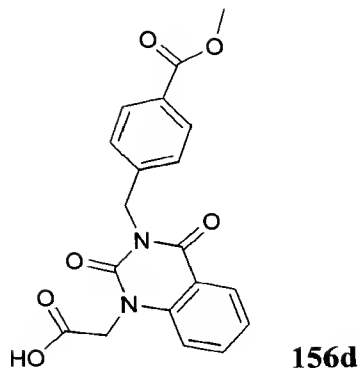
168

**156c**

A solution of compound **156b** (3.2 g, 10.3 mmol) and K_2CO_3 (2.84 g, 20.3 mmol) in CH_3CN (100 mL) was treated with *t*-butyl bromoacetate (2.0 g, 10.3 mmol) and stirred at room temperature for 12 hours. The mixture was filtered and the filtrate was concentrated. The residue was purified by flash chromatography (20% EtOAc in hexanes) to give 4.3 g (99% yield) of compound **156c** as a clear oil:

- 1H NMR ($DMSO-d_6$) δ 1.20 (t, $J = 7.2$ Hz, 3 H), 1.41 (s, 9 H), 1.15 (q, $J = 7.2$ Hz, 2 H), 4.72 (s, 2 H), 4.90 (s, 2 H), 7.31-7.37 (m, 1 H), 7.42 (d, $J = 8.5$ Hz, 3 H), 7.78-7.85 (m, 1 H), 7.88 (d, $J = 8.5$ Hz, 2 H), 8.10 (d, $J = 6.3$, 1 H);
IR (KBr, cm^{-1}) 1746, 1712, 1669;
MS m/e 362 (MH^+);
- Anal. Calcd for $C_{18}H_{22}N_2O_6 \cdot 1.33 H_2O$: C, 61.61; H, 5.99; N, 6.25
Found: C, 61.21; H, 5.59; N, 5.91.

169



A solution of compound **156c** (5.5 g, 14.1 mmol) in TFA (50 mL) was stirred at room temperature for 12 hours. The mixture was concentrated to give
 5 4.3 g (99% yield) of compound **156d** as a white solid:

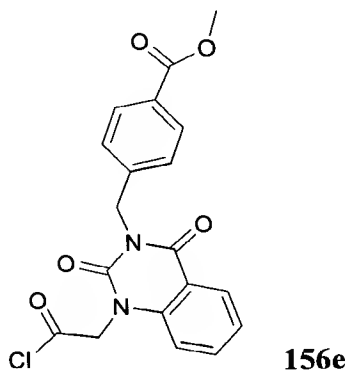
^1H NMR (DMSO- d_6) δ 3.82 (s, 3 H), 4.88 (s, 2 H), 5.21 (s, 2 H), 7.33 (t, J = 7.8 Hz, 1 H), 7.42 (d, J = 8.4 Hz, 3 H), 7.88 (t, J = 7.5 Hz, 1 H), 7.92 (d, J = 7.5 Hz, 2 H), 8.09 (d, J = 7.8 Hz, 1 H);

10 IR (KBr, cm^{-1}) 1712, 1664;

MS m/e 368 (MH^+);

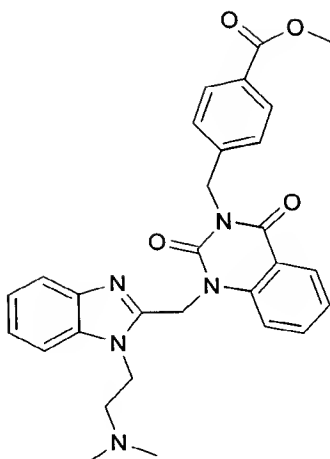
Anal. Calcd for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_6 \cdot 0.94 \text{ H}_2\text{O}$: C, 59.24; H, 4.68; N, 7.27

Found: C, 59.24; H, 4.45; N, 6.88.



15

170

**156**

A solution of compound **156d** (0.5 g, 1.36 mmol) was heated to reflux in thionyl chloride (10 mL) for 30 minutes then cooled and concentrated to give the acid chloride **156e**. The compound **98b** (0.24 g, 1.36 mmol) was dissolved in CH_2Cl_2 (20 mL), cooled to -78°C and treated with the acid chloride **156e** in CH_2Cl_2 (20 mL). The mixture was warmed to room temperature and stirred for 12 hours. The organic layer was washed with saturated aqueous NaHCO_3 , dried, and concentrated. The residue was purified by flash chromatography (CH_2Cl_2 : MeOH = 20:1) to give 0.42 g (49% yield) of a yellow oil. The oil was dissolved in AcOH (50 mL) and heated to reflux for 2 hours then cooled. The excess acetic acid was removed and the residue purified by flash chromatography (CH_2Cl_2 : MeOH = 97:3) to give 0.28 g (70% yield) of compound **156** as a white solid:

^1H NMR ($\text{DMSO}-d_6$) δ 2.95 (s, 6 H), 3.49-3.62 (m, 2 H), 3.83 (s, 3 H), 4.73-4.80 (m, 2 H), 5.26 (s, 2 H), 5.79 (s, 2 H), 7.26 (t, $J = 7.5$ Hz, 1 H), 7.36-7.40 (m, 2 H), 7.48 (d, $J = 7.5$ Hz, 2 H), 7.54-7.64 (m, 2 H), 7.65-7.81 (m, 2 H), 7.90 (d, $J = 7.5$ Hz, 2 H), 8.15 (d, $J = 7.5$ Hz, 1 H);

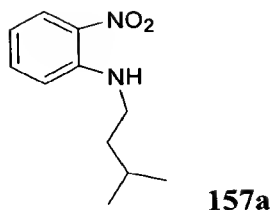
IR (KBr, cm^{-1}) 1711, 1667, 754;

MS m/e 511 (MH^+);

Anal. Calcd for $\text{C}_{29}\text{H}_{29}\text{N}_5\text{O}_4 \cdot 0.97 \text{H}_2\text{O}$: C, 50.16; H, 4.14; N, 8.60

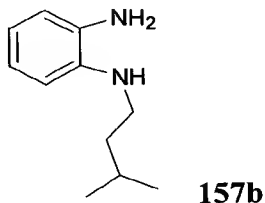
Found: C, 50.16; H, 3.74; N, 8.23.

171



A solution of 2-fluoronitrobenzene (20 g, 142 mmol) and 3-methylbutylamine (12.4 g, 142 mmol) in CH₃CN (100 mL) and Et₃N (28.5 g, 282 mmol) was heated to reflux for 5 days, then cooled and concentrated. The residue was dissolved in EtOAc and washed with 1N HCl. The mixture was dried over MgSO₄ and concentrated to give 27.5 g (93% yield) of compound **157a** as a dark orange oil:

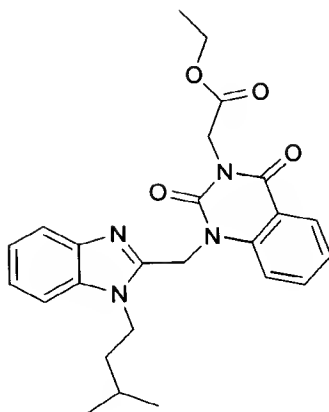
- ¹H NMR (CDCl₃) δ 0.96 (d, J = 6.5 Hz, 6 H), 1.64 (q, J = 7.3 Hz, 2 H), 1.65-1.82 (m, 1 H), 3.26-3.32 (m, 2 H), 6.61 (t, J = 8.3 Hz, 1 H), 6.83 (d, J = 8.4 Hz, 1 H), 7.42 (t, J = 8.0 Hz, 1 H), 8.05 (bs, 1 H, exchanges with D₂O), 8.15 (d, J = 8.7 Hz, 1 H);
MS m/e 208 (MH⁺).



A solution of compound **157a** (6.1 g, 29.3 mmol) in EtOH (50 mL) was reduced by catalytic hydrogenation at 40 psi with 10% palladium on carbon (100 mg) for 4 hours. The catalyst was removed by filtration and the solvent was evaporated to give 5.0 g (99% yield) of compound **157b** as a dark oil:

- ¹H NMR (DMSO-d₆) δ 0.91 (d, J = 6.7 Hz, 6 H), 1.47 (q, J = 7.0 Hz, 2 H), 3.00 (t, J = 7.2 Hz, 2 H), 3.28-3.50 (m, 2 H), 6.37-6.46 (m, 2 H), 6.47-6.53 (m, 2 H);
MS m/e 178 (MH⁺).

172

**157**

Compound **157** was prepared using the same procedures as compound **156** with compounds **157b** and **156e**:

5

^1H NMR (DMSO- d_6) δ 1.00 (d, J = 6.0 Hz, 6 H), 1.20 (t, J = 7.2 Hz, 3 H), 1.63-1.78 (m, 2 H), 4.15 (q, J = 6.9 Hz, 2 H), 4.36 (t, J = 7.5 Hz, 2 H), 4.76 (s, 2 H), 5.70 (s, 2 H), 7.11 (t, J = 7.5 Hz, 1 H), 7.21 (t, J = 7.5 Hz, 1 H), 7.17 (t, J = 7.5 Hz, 1 H), 7.46 (d, J = 7.5 Hz, 1 H), 7.50-7.60 (m, 2 H), 7.78 (t, J = 7.5 Hz, 1 H), 8.18 (d, J = 7.5 Hz, 1 H);

10

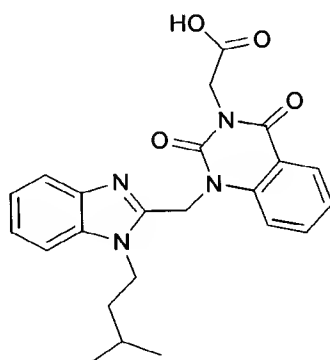
IR (KBr, cm^{-1}) 1742, 1709, 1669, 740;

MS m/e 448 (MH^+);

Anal. Calcd for $\text{C}_{25}\text{H}_{28}\text{N}_4\text{O}_4$: C, 66.95; H, 6.29; N, 12.49

Found: C, 66.76; H, 6.14; N, 12.28.

15

**158**

A mixture of compound **157** (390 mg, 0.87 mmol) and 1N NaOH (0.88 ml, 0.88 mmol) in MeOH (50 mL) was heated to reflux for 4 hours to give a clear solution. The mixture was concentrated and the residue dissolved in 1N HCl and filtered to give 303 mg (83% yield) of compound **158** as a white solid:

5

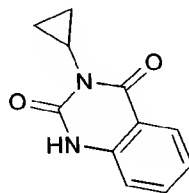
^1H NMR (DMSO- d_6) δ 0.99 (d, J = 5.7 Hz, 6 H), 1.65-1.82 (m, 2 H), 4.25-4.60 (m, 2 H), 4.67 (s, 2 H), 5.88 (s, 2 H), 7.35-7.58 (m, 3 H), 7.48 (t, J = 7.5 Hz, 2 H), 7.79 (t, J = 7.5 Hz, 2 H) 8.16 (d, J = 7.5 Hz, 1 H);

IR (KBr, cm^{-1}) 1711, 1669, 757;

10 MS m/e 420 (MH^+);

Anal. Calcd for $\text{C}_{23}\text{H}_{24}\text{N}_4\text{O}_4 \cdot \text{H}_2\text{O}$: C, 60.97; H, 6.14; N, 12.37

Found: C, 60.59; H, 5.74; N, 12.18.

**159a**

15

Compound **159a** was prepared using the same procedure as compound **156b** starting with cyclopropylamine:

20

^1H NMR (DMSO- d_6) δ 0.70-0.74 (m, 2 H), 0.98-1.02 (m, 2 H), 2.61-2.65 (m, 1 H), 7.11-7.18 (m, 2 H), 7.61 (t, J = 7.5 Hz, 1 H), 7.89 (d, J = 7.9 Hz, 1 H);

IR (KBr, cm^{-1}) 1727, 1666, 1163, 1082;

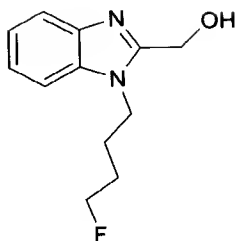
MS m/e 202 (MH^+);

Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_2 \cdot 0.4 \text{H}_2\text{O}$: C, 63.29; H, 5.18; N, 13.42

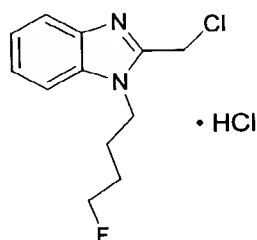
Found: C, 63.55; H, 5.44; N, 13.02.

25

174

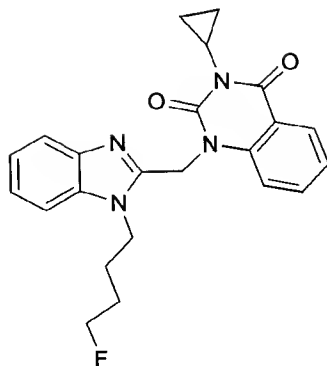
**159b**

- To a solution of 2-hydroxymethylbenzimidazole (1.5 g, 10.12 mmol) in a mixture of DMF and THF (60 mL, 1:1) was added sodium hydride (60% suspension in mineral oil, 425 mg, 10.63 mmol). After stirring for 1 hour at room temperature, 1-bromo-4-fluorobutane (1.56 g, 10.12 mmol) was added and the reaction was stirred at 65 °C for 18 hours. The solvent was evaporated. The residue was diluted with 1N NaOH and extracted with EtOAc. The combined extracts were dried over Na₂SO₄ and evaporated to give 2.34 g (quantitative yield) of compound **159b** as a yellow oil which was used without further purification.

**159c**

- To solution of alcohol **159b** (2.30 g, 10.34 mmol) in CH₂Cl₂ (30 mL) was added thionyl chloride (2.46 g, 20.68 mmol) at 0 °C. The reaction was stirred for 2 hours and then the solvent and excess thionyl chloride were evaporated to give 2.8 g (98% yield) of compound **159c**.

175

**159**

Compound **159** was prepared using the same procedure as compound **4** with compound **159a** and compound **159c**:

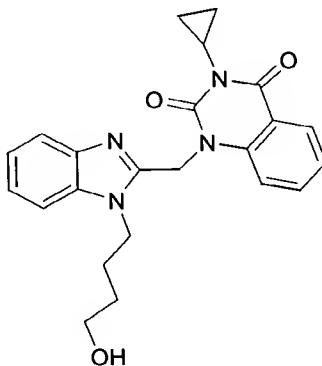
5

^1H NMR (DMSO- d_6) δ 0.73-0.76 (m, 2 H), 1.03-1.09 (m, 2 H), 1.73-1.83 (m, 2 H), 1.86-1.93 (m, 2 H), 2.74-2.79 (m, 1 H), 4.42 (t, J = 7.5 Hz, 2 H), 4.47 (t, J = 6.0 Hz, 2 H), 4.52 (t, 5.1 Hz, 1 H), 5.62 (s, 2 H), 7.11 (t, J = 7.2 Hz, 1 H), 7.22 (t, J = 8.0 Hz, 1 H), 7.23 (t, J = 7.5 Hz, 1 H), 7.27 (t, J = 7.5 Hz, 1 H), 7.47-7.49 (m, 1 H), 7.58 (d, J = 8.0 Hz, 1 H), 7.66 (t, J = 7.6 Hz, 1 H), 8.06 (d, J = 8.0 Hz, 1 H); MS m/e 406 (MH^+);

10

Anal. Calcd for $\text{C}_{23}\text{H}_{23}\text{FN}_4\text{O}_2$: C, 67.96; H, 5.70; N, 13.78

Found: C, 67.57; H, 5.51; N, 13.67

**160**

15

To a solution of compound **159a** (127 mg, 0.63 mmol) in THF (20 mL) was added BTPP (0.6 mL, 1.98 mmol) and the mixture was stirred for 30 minutes at room temperature. Compound **139a** (200 mg, 0.63 mmol) was added and the

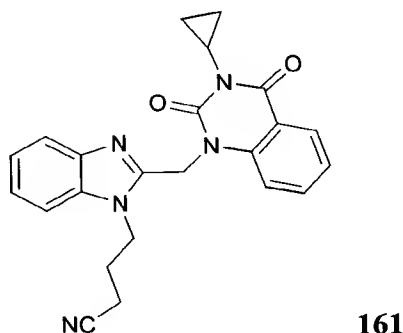
mixture was stirred for 12 hours at room temperature. The solvent was removed. The residue was dissolved in MeOH (5 mL) and diluted with diethyl ether (20 mL) and water (50 mL). After standing for 30 minutes, the precipitated product was isolated by filtration to give 214 mg (84% yield) of compound **160** as a white solid:

^1H NMR (DMSO- d_6) δ 0.73-0.76 (m, 2H), 1.03-1.09 (m, 2H), 1.50-1.56 (m, 2H), 1.79-1.86 (m, 2H), 2.75-2.79 (m, 1H), 3.46 (q, J = 6.3 Hz, 2H), 4.39 (t, J = 7.4 Hz, 2H), 4.52 (t, J = 5.1 Hz, 2H), 5.62 (s, 2H), 7.11 (t, J = 7.2 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 7.27 (t, J = 7.5 Hz, 1H), 7.47-7.49 (m, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.66 (t, J = 7.6 Hz, 1H), 8.06 (d, J = 8.0 Hz, 1H); IR (KBr) 1702, 1664, 1607, 1481;

MS m/e 404 (MH^+);

Anal. Calcd for $\text{C}_{23}\text{H}_{24}\text{N}_4\text{O}_3$: C, 68.30; H, 5.98; N, 13.85

Found: C, 67.99; H, 6.06; N, 13.92.



Compound **161** was prepared using the same method as compound **160** with compound **159a** and compound **25b**:

^1H NMR (DMSO- d_6) δ 0.72-0.75 (m, 2H), 1.02-1.06 (m, 2H), 2.14-2.20 (m, 2H), 2.69 (t, J = 7.4 Hz, 2H), 2.74-2.78 (m, 1H), 4.44 (t, J = 7.5 Hz, 2H), 5.63 (s, 2H), 7.13 (t, J = 7.9 Hz, 1H), 7.22-7.30 (m, 2H), 7.48-7.53 (m, 2H), 7.61 (d, J = 8.1 Hz, 1H), 7.68 (t, J = 7 Hz, 1H), 8.06 (d, J = 7.5 Hz, 1H); IR(KBr) 1708, 1667, 1608;

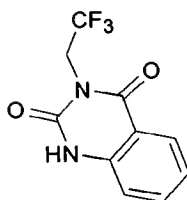
MS m/e 399 (MH^+);

Anal. Calcd for $\text{C}_{23}\text{H}_{21}\text{N}_5\text{O}_2$:

C, 69.15; H, 5.29; N, 17.53

Found:

C, 69.36; H, 5.20; N, 17.56.



162a

5

Compound **162a** was prepared using the same procedure as compound **156b** starting with 2,2,2-trifluoroethylamine hydrochloride:

10 ^1H NMR (DMSO-d_6) δ 4.72 (q, $J = 9.2$ Hz, 2H), 7.20-7.26 (m, 2H), 7.08 (t, $J = 7.6$ Hz, 1H), 7.96 (d, $J = 7.6$ Hz, 1H);

IR (KBr, cm^{-1}) 1727, 1666, 1163, 1082;

MS m/e 244 (MH^+);

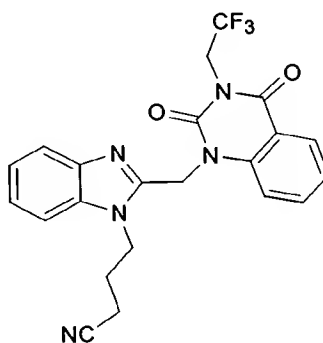
Anal. Calcd for $\text{C}_{10}\text{H}_7\text{F}_3\text{N}_2\text{O}_2$:

C, 49.19; H, 2.89; N, 11.47

15

Found:

C, 49.04; H, 2.85; N, 11.42.



162

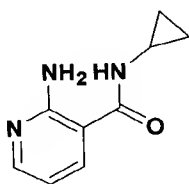
20 Compound **162** was prepared using the same procedure as compound **160** with compound **162a** and compound **25b**:

^1H NMR (DMSO- d_6) δ 2.16-2.18 (m, 2 H), 2.69 (t, J = 7.4 Hz, 2 H), 4.44 (t, J = 7.5 Hz, 2 H), 4.81-4.87 (m, 2 H), 5.71 (s, 2 H), 7.14 (t, J = 7.2 Hz, 1 H), 7.26 (t, J = 7.5 Hz, 1 H), 7.37 (t, J = 7.7 Hz, 1 H), 7.49 (d, J = 8.0 Hz, 1 H), 7.59-7.64 (m, 2 H), 7.78 (t, J = 9.0 Hz, 1 H), 8.15 (d, J = 7.5 Hz, 1 H);

5 MS m/e 441 (MH^+);

Anal. Calcd for $\text{C}_{22}\text{H}_{18}\text{F}_3\text{N}_5\text{O}_2 \cdot 0.4 \text{H}_2\text{O}$: C, 58.93; H, 4.22; N, 15.62

Found: C, 59.21; H, 4.45; N, 15.41.



163a

10

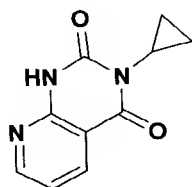
To a solution of 2-aminonicotinic acid (5.0 g, 36.2 mmol), cyclopropylamine (2.0 g, 36.2 mmol), HOBT (4.9 g, 36.2 mmol) in DMF (50 ml) was added EDC (6.9 g, 36.2 mmol) and the mixture stirred for 12h at 23°C. The solvent was removed and the residue dissolved in EtOAc/ H_2O . The organic layer is washed with saturated NaHCO_3 , dried over MgSO_4 and concentrated to give 3.2 g (50%) of product as a white solid.

15

^1H NMR (DMSO- d_6) δ : 0.54-0.59 (m, 2H), 0.66-0.69 (m, 2H), 2.77-2.88 (m, 1H), 3.10-3.40 (br s, 1H), 6.53-6.56 (m, 1H), 7.04 (s, 2H), 7.82 (d, J = 6.2 Hz, 1H), 8.04-8.08 (m, 1H), 8.36-8.42 (m, 1H);

20

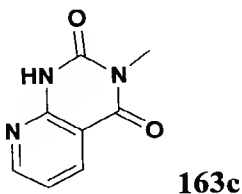
MS m/e 177 (MH^+).



163b

25 Compound **163b** was prepared as described for **156b** except CDI in CH_2Cl_2 was used in place of ethylchloroformate.

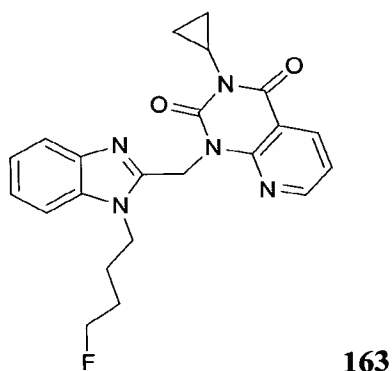
^1H NMR (DMSO- d_6) δ : 0.71-0.77 (m, 2H), 0.99-1.02 (m, 2H), 2.20-2.25 (m, 1H), 7.22-7.24 (m, 2H), 8.25 (dd, J = 1.5, 7.7 Hz, 1H), 8.56-8.58 (m, 1H);
MS m/e 203 (MH^+).



5

Compound **163c** was prepared as described for **163b** except CDI in CH_2Cl_2 was used in place of ethylchloroformate.

10 ^1H NMR (DMSO- d_6) δ : 3.25 (s, 3H), 7.25-7.28 (m, 1H), 8.29 (d, J = 7.8 Hz, 1H), 8.60-8.62 (m, 1H);
MS m/e 177 (MH^+).



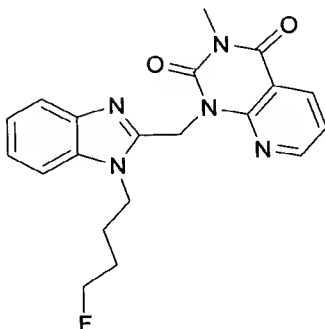
15

3-Cyclopropyl-1-[1-(4-fluorobutyl)-1H-benzimidazol-2-ylmethyl]-1H-pyrido[2,3-d]pyrimidine-2,4-dione, **163**, was prepared as described for compound using **163b** and **159c** with BTPP.

20 ^1H NMR (DMSO- d_6) δ : 0.75-0.79 (m, 2H), 1.04-1.08 (m, 2H), 1.75-1.84 (m, 2H), 1.91-1.96 (m, 2H), 2.76-2.79 (m, 1H), 4.42-4.48 (m, 2H), 4.53 (dt, J = 9.7, 41.5 Hz, 2H), 7.11 (t, J = 7.7 Hz, 1H), 7.21 (t, J = 7.7 Hz, 1H), 7.32-7.35 (m,

1H), 7.44 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 8.42 (dt, J = 1.7, 7.7 Hz, 1H), 8.58-8.59 (m, 1H);

MS m/e 407 (MH⁺).

**163d**

3-Methyl-1-[1-(4-fluorobutyl)-1H-benzimidazol-2-ylmethyl]-1H-pyrido[2,3-d]pyrimidine-2,4-dione, **163d**, was prepared as described for compound using 3-methyl-1H-pyrido[2,3-d]pyrimidine-2,4-dione **163c** and **159c** with BTPP.

¹H NMR (DMSO-d₆) δ: 1.75-1.83 (m, 2H), 1.93-1.97 (m, 2H), 3.37 (s, 3H), 4.43-4.49 (m, 3H), 4.57 (t, J = 5.9 Hz, 1H), 5.74 (s, 2H), 7.10 (t, J = 7.5 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 7.36-7.44 (m, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 8.47 (d, J = 7.8 Hz, 1H), 8.62 (d, J = 4.8 Hz, 1H);

MS m/e 381 (MH⁺).

**164a**

To a -78°C mixture of cyclopropylamine (10 g, 1.75 mmol) in CH₂Cl₂ (100 mL) was added a solution of 2-nitrobenzene sulfonyl chloride (22.1 g, 85.7 mmol) and the mixture was stirred for 12 h. The mixture was washed with 1N HCl dried over MgSO₄ then concentrated to give 18.7 g, (88%) of a N-Cyclopropyl-2-nitrobenzenesulfonamide as a tan solid.

$^1\text{H NMR}(\text{CDCl}_3)$ δ : 0.66-0.70 (m, 2H), 0.70-0.75 (m, 2H), 2.32-2.37 (m, 1H), 5.58 (s, 1H), 7.13-7.78 (m, 2H), 7.83-7.87 (m, 1H), 8.18-8.22 (m, 3H); MS m/e 242 (MH^+).

**164b**

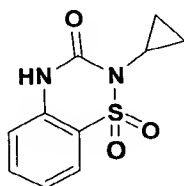
5

A solution of N-cyclopropyl-2-nitro-benzenesulfonamide (7.9 g, 33.0 mmol) in EtOH (50 ml) was treated with HCl (3.0 ml, 4.0 N in dioxane), Pd/C (10%, 100 mg) and shaken in a Parr Hydrogenator at 50 psi for 48 h. The catalyst was removed by filtration and the solvent evaporated to give 6.9 g (84%) of 2-Amino-N-cyclopropyl-benzenesulfonamide as a light grey solid.

10

$^1\text{H NMR}$ (DMSO-d_6) δ : 0.35-0.37 (m, 2H), 0.42-0.44 (m, 2H), 2.0-2.08 (m, 1H), 5.89 (s, 2H), 6.62 (t, $J = 7.1$ Hz, 1H), 6.80 (d, $J = 8.3$ Hz, 1H), 7.27 (t, $J = 7.1$ Hz, 1H), 7.50 (d, $j = 8.0$, 1H), 7.82 (s, 1H); MS m/e 242 (MH^+).

15

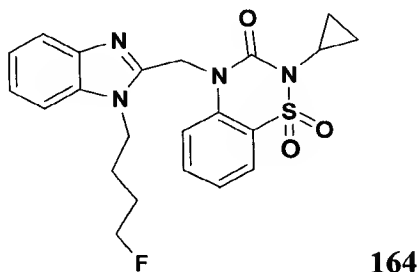
**164c**

A solution of 2-amino-N-cyclopropyl-benzenesulfonamide (6.9 g, 32.5 mmol) in CH_2Cl_2 (50 ml) was treated with CDI (6.5 g, 40 mmol) and stirred for 12 h at reflux. The solution was washed with HCl (1N), dried over MgSO_4 and concentrated to give 6.5 g (84%) of 2-cyclopropyl-1,1-dioxo-1,4-dihydro-2H-1λ⁶-benzo[1,2,4]thiadiazin-3-one as a brown solid.

25

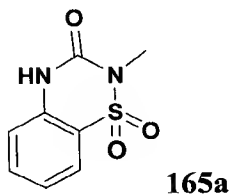
¹H NMR (DMSO-d₆) δ: 0.72-0.80 (m, 2H), 0.90-1.1 (m, 2H), 2.71-2.75 (m, 1H), 7.23 (d, 8.1 Hz, 1H), 7.29 (t, J = 7.7 Hz, 1H), 7.68 (t, J = 7.5 Hz, 1H), 7.81 (d, J = 7.6 Hz, 1H);
MS m/e 238 (MH⁺).

5



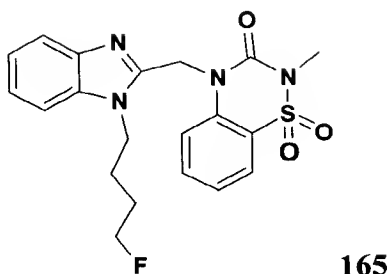
2-Cyclopropyl-4-[1-(4-fluorobutyl)-1H-benzimidazol-2-ylmethyl]-1,1-dioxo-1,4-dihydro-2H-1λ⁶-benzo[1,2,4]thiadiazin-3-one as described for compound **25** using **159c** and **164c**.

¹H NMR (DMSO-d₆) δ: 0.90-0.96 (m, 2H), 1.06-1.10 (m, 2H), 1.80-1.91 (m, 2H), 2.07-2.13 (m, 2H), 2.91-2.93 (m, 1H), 4.43 (t, J = 8.0 Hz, 2H), 4.54 (dd, J = 5.5, 47.1 Hz, 2H), 6.03 (s, 2H), 7.26 (s, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.52-7.54 (m, 2H), 7.69 (t, J = 7.8 Hz, 1H), 7.80 (d, J = 8.6 Hz, 1H), 7.86 (d, J = 7.7 Hz, 1H), 7.91-7.93 (m, 1H);
MS m/e 443 (M⁺).



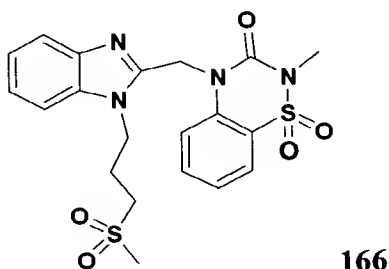
2-Methyl-1,1-dioxo-1,4-dihydro-2H-1λ⁶-benzo[1,2,4]thiadiazin-3-one was prepared as described above for compound **164c** except phosgene was used in place of CDI for the ring closure reaction.
¹H NMR (DMSO-d₆) δ: 3.34 (s, 3H), 7.27-7.34 (m, 2H), 7.71 (t, J = 7.0 Hz, 1H), 7.86 (d, J = 7.5 Hz, 1H);

MS m/e 212 (MH⁺).



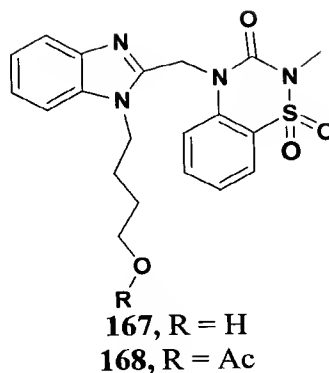
- 5 Prepared from **165a** and **159c** as described for compound **25**.

¹H NMR (DMSO-d₆) δ: 1.74-1.82 (m, 2H), 1.88-1.93 (m, 2H), 3.24 (s, 3H), 4.38 (t, J = 7.3 Hz, 2H), 4.51 (dt, J = 5.9, 47.4 Hz, 2H), 5.57 (s, 2H), 7.15 (t, J = 7.5 Hz, 1H), 7.24 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.8 Hz, 1H), 7.51 (d, J = 7.9 Hz, 1H),
10 7.44-7.47 (m, 2H), 7.78 (t, J = 8.1 Hz, 1H), 7.99 (d, J = 7.5 Hz, 1H);
MS m/e 416 (MH⁺).



- 15 A mixture of 2-methyl-1,1-dioxo-1,4-dihydro-2H-1,4-benzo[1,2,4]thiadiazin-3-one (300 mg, 0.71 mmol) and Cs₂CO₃ (0.69, 2.13 mmol) in DMF (20 mL) was stirred for 30 minutes and then treated with **10d** (0.23 g, 0.71 mmol) and stirred for 12 h. The mixture is filtered and concentrated. The residue was purified by preparative thin layer chromatography using 50% EtOAc in hexanes as eluant to
20 give 48 mg (15%) of the product **166** as a clear glass.

¹H NMR (DMSO-d₆) δ: 2.10-2.35 (m, 2H), 2.73 (s, 3H), 2.89 (s, 3H), 3.31-3.39 (m, 2H), 4.40-4.54 (m, 2H), 5.58 (s, 2H);
MS m/e 462 (MH⁺).



5

2-methyl-1,1-dioxo-1,4-dihydro-2H-116-benzo[1,2,4]thiadiazin-3-one (300 mg, 0.71 mmol) and Cs_2CO_3 (0.69, 2.13 mmol) in DMF (20 mL) was stirred for 30 minutes and then treated **139a** (224 mg, 0.71 mmol) and stirred for 12 h. The mixture was filtered and concentrated. The residue was purified by preparative

10 TLC using 30% EtOAc/hexanes as eluant to give **168**, 48 mg (15%) of the acetate and **167**, 70 mg (24%) of the alcohol. The alcohol could be obtained exclusively by treating the crude reaction mixture with HCl (1N, 10 ml) in MeOH and heating the mixture to reflux for 2 h. Preparative TLC of this reaction gave 147 mg (50%) of **167**.

15 **168**, R = Ac

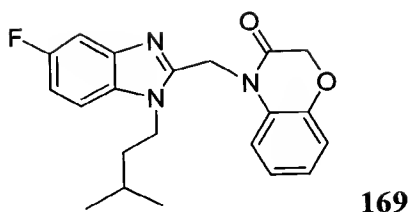
^1H NMR (DMSO- d_6) δ : 1.66-1.74 (m, 2H), 1.85-1.89 (m, 2H), 2.00 (s, 3H), 3.24 (s, 3H), 4.07 (t, $J = 6.5$ Hz, 2H), 4.37 (t, $J = 7.2$ Hz, 2H), 5.57 (s, 2H), 7.15 (d, $J = 7.9$ Hz, 1H), 7.24 (t, $J = 7.2$ Hz, 1H), 7.45 (t, $J = 7.6$ Hz, 1H), 7.51 (d, $J = 7.9$ Hz, 1H), 7.60 (t, $J = 7.2$ Hz, 1H), 7.78 (t, $J = 7.3$ Hz, 2H), 7.99 (d, $J = 7.9$ Hz, 1H);

20 MS m/e 456 (MH^+).**167**, R = H:

^1H NMR (DMSO- d_6) δ : 1.52-1.55 (m, 2H), 1.81-1.89 (m, 2H), 3.24 (s, 3H), 3.41-3.52 (m, 2H), 4.35 (t, $J = 7.5$ Hz, 2H), 4.50 (t, $J = 5.1$ Hz, 1H), 5.57 (s, 2H), 7.14 (t, $J = 8.0$ Hz, 1H), 7.23 (t, $J = 7.2$ Hz, 1H), 7.45 (t, $J = 7.7$ Hz, 1H), 7.50 (d, $J = 7.9$ Hz, 1H), 7.55-7.61 (m, 2H), 7.77 (t, $J = 7.2$ Hz, 1H), 7.99 (d, $J = 6.6$ Hz, 1H);

25 MS m/e 456 (MH^+).

185

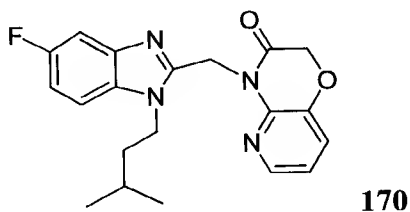


Compound **169** was prepared using the same procedure as compound **160** with 2H-1,4-benzoxazin-3(4*H*)-one and compound **42d**:

5

^1H NMR (CD_3OD) δ 1.04 (d, J = 6.2 Hz, 6H), 1.76-1.78 (m, 3H), 4.45-4.48 (m, 2H), 4.78 (s, 2H), 5.63 (s, 2H), 7.03-7.09 (m, 3H), 7.14-7.16 (m, 1H), 7.32 (dt, J = 2.4, 9.2 Hz, 1H), 7.39 (dd, J = 2.4, 8.5 Hz, 1H), 7.75 (dd, J = 4.2, 9.1 Hz, 1H); MS m/e 368 (MH^+).

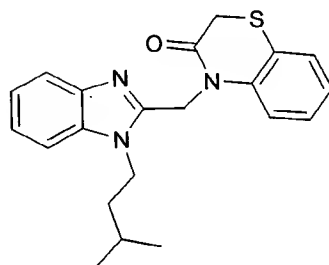
10



Compound **170** was prepared using the same procedure as compound **160** with 2H-pyrido[3,2-B]-1,4-oxazin-3(4*H*)-one and compound **42d**:

15

^1H NMR (CD_3OD) δ 1.06 (d, J = 6.4 Hz, 6 H), 1.80-1.88 (m, 3 H), 4.56-4.60 (m, 2 H), 4.90 (s, 2 H), 5.76 (s, 2 H), 7.08 (dd, J = 4.9, 8.0 Hz, 1 H), 7.34-7.43 (m, 3 H), 7.82 (dd, J = 4.3, 9.1 Hz, 1 H), 7.92 (dd, J = 1.3, 4.9 Hz, 1 H); MS m/e 369 (MH^+).



20

A solution of the compound **4b** (0.5 g, 2.29 mmol) and 2H-1,4-benzothiazin-3(4H)-one (0.38 g, 2.29 mmol) containing tributylphosphine (0.61 g, 3.0 mmol) in benzene (5 ml) was treated with 1,1'-(azodicarbonyl)dipiperidine (0.76 g, 3.0 mmol). The mixture was stirred at room temperature for 12 hours.

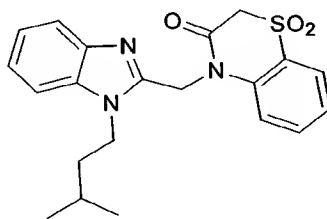
- 5 The solvent was removed. The residue was purified by flash chromatography (15% EtOAc in hexanes) and further purified by preparative HPLC (C18, gradient 30% MeOH/Water to 90% MeOH/water with 0.1% TFA) to give 150 mg (20% yield) of compound **171** as a white solid:

¹H NMR (DMSO-d₆) δ 0.97 (d, J = 6.2 Hz, 6 H), 1.6-1.8 (m, 3 H), 3.33 (s, 2 H),
10 3.61 (s, 2 H), 3.41-4.13 (m, 2 H), 5.43 (s, 2 H), 7.01 (t, J = 7.5 Hz, 1 H), 7.14-7.27 (m, 3 H), 7.41 (t, J = 7.5, 2 H), 7.52 (t, J = 7.9 Hz, 2 H);

IR (KBr, cm⁻¹) 2955, 1673, 1479, 1449, 1384, 741;

MS m/e 365 (MH⁺);

Anal. Calcd for C₂₁H₂₃N₃OS: C, 69.01; H, 6.34; N, 11.50
15 Found: C, 68.84; H, 6.31; N, 11.45.

**172**

- A solution of compound **171** (300 mg, 0.8 mmol) and 3-chloroperbenzoic
20 acid (80%, 350 mg, 1.64 mmol) in CH₂Cl₂ (20 ml) was stirred at room temperature for 12 hours. The reaction mixture was washed with saturated aqueous NaHSO₃ and saturated aqueous NaHCO₃ then dried over MgSO₄ and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc = 3:2) to give 60 mg (18% yield) of compound **172** as a white solid:

25

¹H NMR (DMSO-d₆) δ 0.98 (d, J = 6.1 Hz, 6 H), 1.60-1.73 (m, 3 H), 4.26-4.34 (m, 2 H), 5.00 (s, 2 H), 5.52 (s, 2 H), 7.13-7.27 (m, 2 H), 7.41 (t, J = 7.0 Hz, 1 H), 7.54 (t, J = 8.1 Hz, 2 H), 7.73-7.79 (m, 2 H), 7.91 (d, J = 7.7 Hz, 1 H);

187

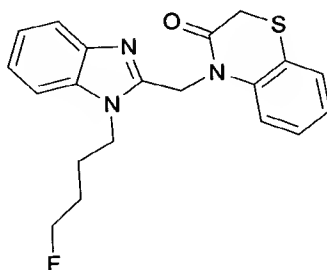
IR (KBr, cm^{-1}) 2954, 1692, 1482, 1319, 1171, 738;

MS m/e 397 (MH^+);

Anal. Calcd for $\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_3\text{S}$: C, 63.46; H, 5.83; N, 10.57

Found: C, 63.17; H, 5.86; N, 10.30.

5



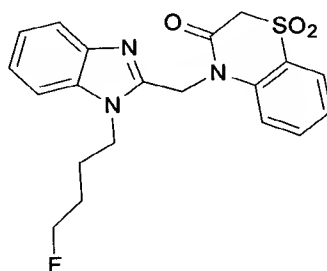
173

Compound 173 was prepared as described for compound **25** with **159c** and 2H-1,4-benzothiazin-3(4H)-one using BTPP.

10

^1H NMR ($\text{DMSO}-d_6$) δ : 1.77-1.85 (m, 2H), 1.92-1.97 (m, 2H), 3.50 (s, 2H), 4.30 (t, $J = 7.6$ Hz, 1H), 4.49 (dt, $J = 5.8, 47.1$ Hz, 2H), 5.52 (s, 2H), 7.00 (t, $J = 8.0$ Hz, 1H), 7.22-7.28 (m, 5H), 7.32-7.34 (m, 1H), 7.72 (t, $J = 7.9$ Hz, 1H);
MW m/e 369 (MH^+).

15



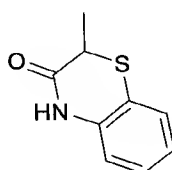
174

To a solution of sulfide (200 mg, 0.54 mmol) in DMF (20 ml) was treated with MPP (560 mg, 1.14 mmol) and stirred for 12 h. The solvent was removed and the residue was dissolved in EtOAc/ H_2O . The organic layer was washed with saturated NaHCO_3 , then dried over MgSO_4 and concentrated to give 60 mg

20

(30%), of 4-[1-(4-fluoro-butyl)-1H-benzimidazol-2-ylmethyl]-1,1-dioxo-1,4-dihydro-2H-1λ⁸-benzo[1,4]thiazin-3-one.

¹H NMR (DMSO-d₆) δ: 1.73-1.81 (m, 2H), 1.86-1.92 (m, 2H), 4.38 (t, J = 5.8 Hz, 2H), 4.50 (dt, J = 6.0, 47.3 Hz, 2H), 4.99 (s, 2H), 5.53 (s, 2H), 7.17 (t, J = 7.6 Hz, 1H), 7.25 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.7 (t, J = 8.1 Hz, 1H), 7.91 (d, J = 7.7 Hz, 1H); MS m/e 401 (MH⁺).

**175a**

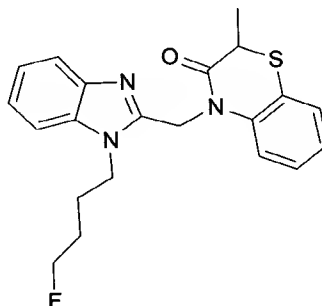
10

To a mixture of 2-bromopropionic acid (1.21 g, 8.0 mmol), 2-aminothiophenol (1.0 g, 8.0 mmol), HOBT (1.1g, 8.0 mmol) in DMF (50 ml) was added EDC (1.53 g, 8.0 mmol) and the mixture stirred for 12 h then concentrated. The residue was dissolved in EtOAc/H₂O. The organic layer was washed with saturated NaHCO₃, dried over MgSO₄ and concentrated. The residue solidified on standing to give the product 0.72 g, (50%) as a tan solid.

15

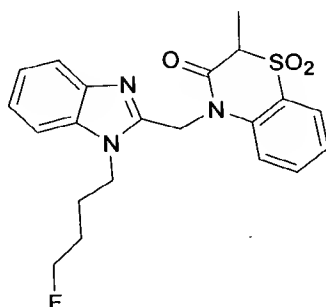
¹H NMR (DMSO-d₆) δ: 1.32 (d, J = 11.7Hz, 3H), 3.65 (q, J = 7.0 Hz, 1H), 6.96-6.99 (m, 2H), 7.18 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H);

20 MS m/e 178 (MH⁺).

**175**

Compound **175** was prepared as described for compound **25** using compound **175a** and **159c** with BTTP instead of Cs_2CO_3 .

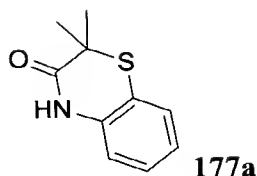
^1H NMR (DMSO- d_6) δ : 1.37 (d, $J = 6.9$ Hz, 1H), 1.71-1.80 (m, 2H), 1.83-1.87 (m, 2H), 3.76 (q, $J = 6.8$ Hz, 1H), 4.33-4.37 (m, 2H), 4.49 (dt, $J = 6.0, 4.7$ Hz, 2H), 5.35 (d, $J = 16.8$ Hz, 1H), 5.49 (d, $J = 16.8$ Hz, 1H), 7.07 (t, $J = 7.6$ Hz, 1H), 7.16 (t, $J = 7.2$ Hz, 1H), 7.21-7.28 (m, 2H), 7.42 (t, $J = 6.4$ Hz, 2H), 7.54 (d, $J = 8.0$ Hz, 1H), 7.58 (d, $J = 8.0$ Hz, 1H);
MS m/e 383 (MH^+).

**176**

To a solution of sulfide (1.64 g, 0.43 mmol) in DMF (20 ml) was treated with MPP (4.45 mg, 0.90 mmol) and stirred for 12 h. The solvent was removed and the residue was dissolved in EtOAc/ H_2O . The organic layer was washed with saturated NaHCO_3 , then dried over MgSO_4 and concentrated. The yellow oil was purified by preparative TLC to give **176** 60 mg (30%), as a yellow oil.

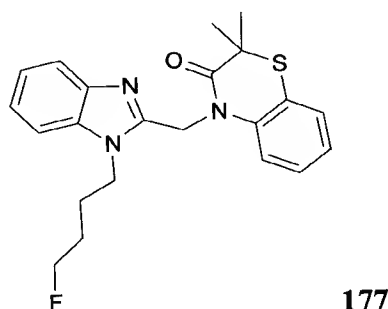
^1H NMR (DMSO- d_6) δ : 1.48 (d, $J = 6.9$ Hz, 3H), 1.65-1.79 (m, 2H), 1.80-1.95 (m, 2H), 4.30-4.45 (m, 2H), 4.50 (dt, $J = 5.9, 4.7$ Hz, 2H), 5.03 (q, $J = 6.9$ Hz, 1H), 5.40 (d, $J = 17$ Hz, 1H), 5.64 (d, $J = 17$ Hz, 1H), 7.17 (t, 7.6 Hz, 1H), 7.25 (t, $J = 8.0$ Hz, 1H), 7.45 (t, $J = 7.3$ Hz, 1H), 7.52 (d, $J = 8.0$ Hz, 1H), 7.60 (d, $J = 8.0$ Hz, 1H), 7.68 (d, $J = 8.4$ Hz, 1H), 7.78 (t, $J = 8.2$ Hz, 1H), 7.93 (d, $J = 7.6$ Hz, 1H);
MS m/e 415 (MH^+).

190



To a slurry of NaH (0.64 g, 16 mmol) in DMF (20 ml) was added 2-aminothiophenol (2.0 g, 16 mmol) and the mixture stirred until gas evolution ceased. 2-methyl-2-bromopropionic acid ethyl ester (3.12 g, 2.34 ml, 16 mmol) and the mixture stirred for 8 h. The solvent was removed and the residue dissolved in toluene and heated to reflux for 12 h. The solvent was removed to give **177a** 2.87 g (92 %) as a tan solid.

¹H NMR (DMSO-d₆) δ: 1.49 (s, 6H), 6.88 (d, J = 8 Hz, 1H), 7.01 (t, J = 7.5 Hz, 1H), 7.17 (t, J = 6.7 Hz, 1H), 7.26-7.29 (m, 1H), .72 (br s, 1H); MS m/e 193 (MH⁺).

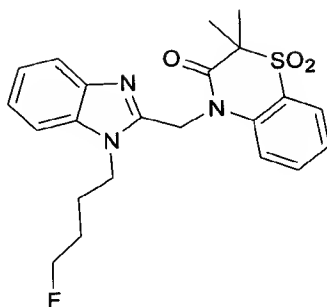


15

Compound **177** was prepared as described for compound **25** using **159c** and **177a** with BTPP instead of Cs₂CO₃.

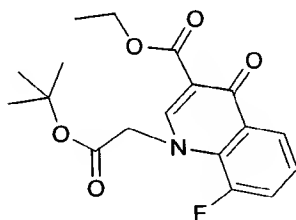
¹H NMR (DMSO-d₆) δ: 1.39 (s, 6H), 1.73-1.79 (m, 2H), 1.85-1.88 (m, 2H), 4.35 (t, J = 7.1 Hz, 2H), 4.50 (dt, J = 5.7, 47.3 Hz, 2H), 5.43 (s, 2H), 7.08 (t, J = 7.5 Hz, 1H), 7.15 (t, J = 7.8 Hz, 1H), 7.22 (t, J = 7.2 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 7.40 (t, J = 8.9 Hz, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.57 (d, J = 7.9 Hz, 1H); MS m/e 397 (MH⁺).

191

**178**

4-[1-(4-Fluoro-butyl)-1H-benzimidazol-2-ylmethyl]-2,2-dimethyl-1,1-dioxo-
1,4-dihydro-2H-1λ⁶-benzo[1,4]thiazin-3-one was prepared as described for
5 compound **176** above.

¹H NMR (DMSO-d₆) δ: 1.50 (s, 6H), 1.75-1.80 (m, 2H), 1.89-1.92 (m, 2H), 4.37
(t, J = 7.3 Hz, 1H), 4.51 (dt, J = 5.9, 47.4 Hz, 2H), 5.52 (s, 2H), 7.15 (t, J = 7.9
Hz, 1H), 7.24 (t, J = 7.7 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.49 (d, J = 7.9 Hz,
10 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.76 (t, J = 7.6 Hz, 1H),
7.95 (d, J = 7.7 Hz, 1H);
MS m/e 429 (MH⁺).

**179a**

15

To a slurry of sodium hydride (0.44g, 8.50 mmol) in DMF (50 mL) was
added ethyl 1,4-dihydro-8-fluoro-4-oxoquinoline-3-carboxylate [Maybridge](2.0
g, 8.50 mmole) and the mixture was stirred until gas evolution ceased. *T*-butyl
bromoacetate (1.75 g, 9.00 mmol) was added and the mixture was stirred for 12
20 hours at room temperature. The solvent was removed. The residue was dissolved
in EtOAc and washed with water. The organic extracts were dried with MgSO₄

and evaporated. The residue was purified by flash chromatography (3% MeOH/CH₂Cl₂) to give 2.35 g (79% yield) of compound **179a** as a white solid:

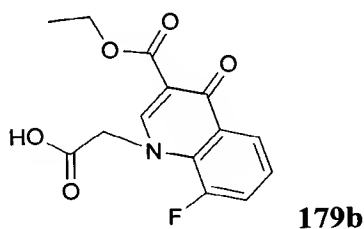
¹H NMR (DMSO-d₆) δ 1.29 (t, J = 6.9 Hz, 3 H), 1.43 (s, 3 H), 4.24 (q, J = 6.9 Hz, 2 H), 5.21 (d, J = 7.5 Hz, 2 H), 7.44-7.49 (m, 1 H), 7.65 (dd, J = 7.8, 16.0 Hz, 1 H), 8.10 (d, J = 7.2 Hz, 1 H), 8.65 (s, 1 H);

IR (KBr, cm⁻¹) 1739, 1722, 1243;

MS m/e 349 (MH⁺);

Anal. Calcd for C₁₈H₂₀FNO₅: C, 61.88; H, 5.77; N, 4.01

Found: C, 61.73; H, 5.69; N, 4.08.



Compound **179a** (2.0 g, 5.70 mmol) was stirred with TFA (20 mL) for 12 hours then concentrated to give an oil. The oil was triturated with water and filtered to give 1.6 g (99% yield) of compound **179b** as a tan solid:

¹H NMR (DMSO-d₆) δ 1.29 (t, J = 7.1 Hz, 3 H), 4.25 (d, J = 7.1 Hz, 2 H), 5.24 (d, J = 4.4 Hz, 2 H), 7.44-7.48 (m, 1 H), 7.47 (dd, J = 7.9, 16 Hz, 1 H), 8.09 (d, J = 7.9 Hz, 1 H), 8.66 (s, 1 H);

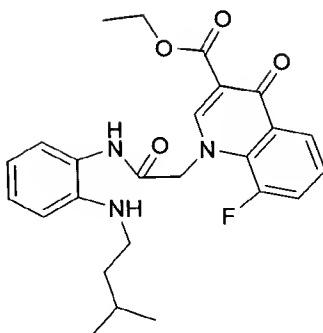
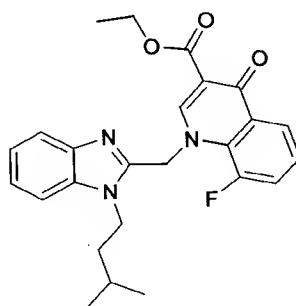
IR (KBr, cm⁻¹) 1728, 1688;

MS m/e 293 (MH⁺);

Anal. Calcd for C₁₄H₁₂FNO₅: C, 56.43; H, 4.20; N, 4.73

Found: C, 56.43; H, 4.15; N, 4.75.

193

**179c****179**

5 To a mixture of compound **179b** (1.5g, 1.70 mmol) and 2-chloro-1-methyl
pyridinium iodide (0.522, 2.04 mmol) in CH₃CN (50 ml) was added triethylamine
(0.48 ml, 1.70 mmol) followed by compound **157b** (0.3 g, 1.70 mmol). The
mixture was stirred for 12 hours at room temperature. The reaction mixture was
filtered to give 0.44 g (57%) of the intermediate **179c** as a white solid. The solid
10 (0.44 g, 0.97 mmol) was dissolved in AcOH (25 ml) and heated to reflux for 4
hours then cooled and concentrated. The residue was purified by flash
chromatography (3% MeOH in CH₂Cl₂) to give 289 mg (69% yield) of
compound **179** as a white solid:

15 ¹H NMR (DMSO-d₆) δ 1.02 (d, J = 5.7 Hz, 6 H), 1.29 (t, J = 6.9 Hz, 3 H), 1.68-
1.72 (m, 3 H), 4.22-4.31 (m, 4 H), 6.09 (d, J = 4.5 Hz, 2 H), 7.12 (t, J = 7.5 Hz, 1
H), 7.24 (t, J = 7.5 Hz, 1 H);

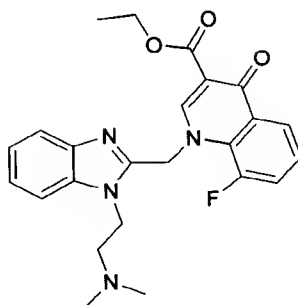
IR (KBr, cm⁻¹) 2958, 1718, 1610, 1561, 1260, 1129;

MS m/e 435 (MH⁺);

20 Anal. Calcd for C₂₅H₂₆FN₃O₃•0.64 H₂O: C, 67.17; H, 6.15; N, 9.40

194

Found: C, 67.17; H, 6.14; N, 9.12.

**180**

5 Compound **180** was prepared as a tan foam using the same procedure as compound **179** with compound **179b** and compound **98b** in 51% yield:

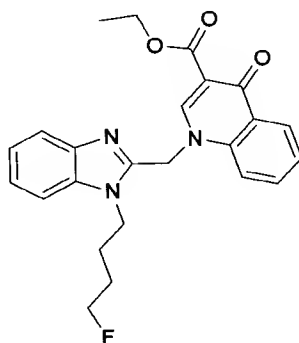
¹H NMR (DMSO-d₆) δ 1.29 (t, J = 7.2 Hz, 3 H), 2.27 (s, 6 H), 2.66 (t, J = 6.3 Hz, 2 H), 4.25 (q, J = 7.2 Hz, 2 H), 4.38 (t, J = 6.3 Hz, 2 H), 6.09 (s, 2 H), 7.09 (t, J = 7.2 Hz, 1 H), 7.15 (t, J = 7.2 Hz, 1 H), 7.40-7.52 (m, 4 H), 8.13 (d, J = 9 Hz, 1 H), 8.78 (s, 1 H);

IR (KBr, cm⁻¹) 1725, 1695;

MS m/e 436 (MH⁺);

Anal. Calcd for C₂₄H₂₅FN₄O₃•0.72 H₂O: C, 64.16; H, 5.93; N, 12.47

15 Found: C, 64.15; H, 5.84; N, 12.11.

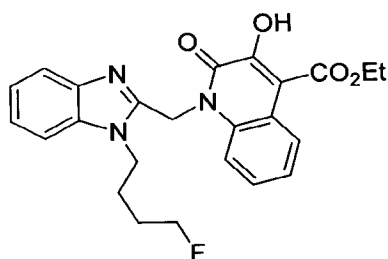
**181**

Compound **181** was prepared as described for compound **25** using **159c** and 4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (prepared as described by

20

Gould, R. G.; Jacobs, W. A.; *J. Am. Chem. Soc.* **1939**, *61*, 2890) using BTPP as described for compound **25**.

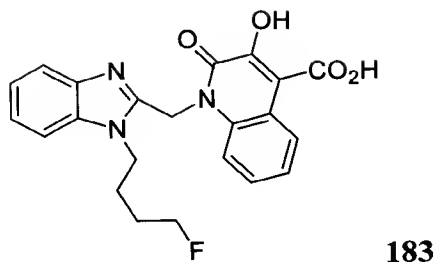
¹H NMR (DMSO-d₆) δ: 1.29 (t, J = 7.1 Hz, 2H), 1.70-1.84 (m, 4H), 4.25 (q, J = 7.1 Hz, 1H), 4.42-4.48 (m, 3H), 4.56 (dt, J = 5.9, 47 Hz, 1H), 6.06 (s, 2H), 7.15 (t, J = 7.3 Hz, 1H), 7.24 (t, J = 7.3 Hz, 1H), 7.44-7.49 (m, 2H), 7.62-7.66 (m, 3H), 8.26 (d, J = 7.9 Hz, 1H), 8.93 (s, 1H); MS m/e 421 (MH⁺).

**182**

A solution containing the isatin **114a** (215 mg, 0.61 mmol), diethyl amine (63 μL, 0.61 mmol) and ethyl diazoacetate (128 μL, 1.22 mmol) in DMF-EtOH (1:1, 6 mL) was stirred at room temperature for 15 hours. The solvents were removed *in vacuo* and to the residue was added 1M HCl (10 mL). After stirring for 30 min. the mixture was extracted with ethyl acetate (2x15 mL). The aqueous phase was neutralized with solid NaHCO₃ and extracted with ethyl acetate (2x 15 mL). The organic phases were combined and washed with brine (10 mL), and dried (MgSO₄) to give **182** (294 mg, 100%) as a yellow solid.

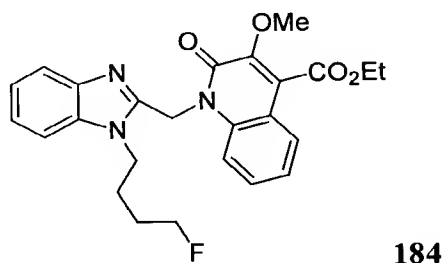
¹H NMR (CDCl₃) δ 8.85 (br s, 1H), 8.16 (d, J = 8.5 Hz, 1H), 7.88 (d, J = 7.7 Hz, 1H), 7.79 (m, 1H), 7.46 (t, J = 7.3 Hz, 1H), 7.32 (m, 4H), 6.04 (s, 2H), 4.55 (q, J = 7.1 Hz, 2H), 4.40 (dt, J = 5.6, 47 Hz, 2H), 4.31 (t, J = 7.6 Hz, 2H), 1.68 (m, 4H), 1.47 (t, J = 7.1 Hz, 3H); MS m/e 438 (MH⁺).

196



A mixture of the ethyl ester **182** (294 mg, 0.672 mmol) in water (5 mL), 1M NaOH (3.4 mL), dioxane (4mL) was heated at reflux temperature for 3 hours. 1M NaOH (5 mL) was added and heating was continued for 1 hour. The mixture was cooled to room temperature and acidified to pH 3 with 1 M HCl. Extraction with ethyl acetate (4x 20 mL) and washing with brine (10 mL), drying (MgSO₄) afforded the pure **183**, 150 mg (55%) as a white solid.

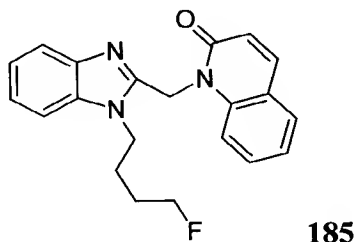
¹H NMR (DMSO) δ 7.61 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.31 (t, J = 7.7 Hz, 1H), 7.23 (m, 2H), 7.14 (t, J 7.5 Hz, 1H), 5.88 (s, 2H), 4.50 (m, 4H), 1.80 (m, 4H); MS m/e 410 (MH⁺).



To a solution of the quinolone **182** (52 mg, 0.12 mmol) in DMF (2 mL) was added Cs₂CO₃ (82 mg, 0.25 mmol). After stirring for 5 min. MeI (9.0 μL, 0.14 mmol) was added and stirring was continued for 4 hours. The volatiles were removed *in vacuo* and the residue suspended in water. The product was extracted into ethyl acetate (2x 12 mL), the combined organic fractions washed with brine (5 mL) and dried (MgSO₄). Purification by flash column chromatography (eluent 2% methanol in methylene chloride) gave 21 mg (39%) of **184** as a white solid.

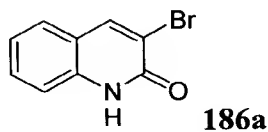
^1H NMR (CDCl_3) δ 8.17 (d, J = 8.6 Hz, 1H), 7.76 (m, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.27 (m, 4H), 5.92 (s, 2H), 4.51 (q, J = 7.2 Hz, 2H), 4.40 (m, 4H), 4.06 (s, 3H), 1.67 (m, 4H), 1.44 (t, J = 7.2 Hz, 3H);
MS m/e 452 (MH^+).

5

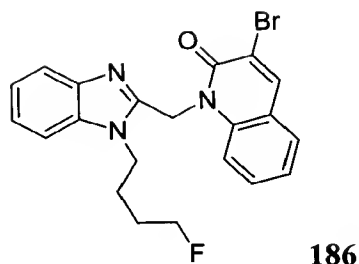


Compound **185** was prepared as described for compound **25** from 2-hydroxyquinoline (52 mg, 0.36 mmol) and compound **159c**. Compound **185** was
10 obtained after purification by flash column chromatography (eluent 2% methanol in methylene chloride) to give 60 mg (48%) of **185** as an off-white solid.

^1H NMR (DMSO) δ 8.02 (d, J = 9.5 Hz, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.62 (d, J = 8.6 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.55 (t, J = 8.2 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 7.3 Hz, 1H), 7.22 (t, J = 7.3 Hz, 1H), 7.13 (t, J = 7.3 Hz, 1H),
15 6.70 (d, J = 9.5 Hz, 1H), 5.80 (s, 2H), 4.49 (m, 4H), 1.80 (m, 4H);
MS m/e 350 (MH^+).

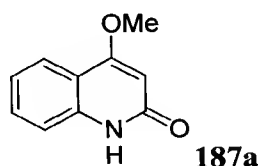


20 Compound **186a** was prepared according to the procedure reported by Sabol *et al.*, *Synth. Commun.*, **2000**, 30, 427-432.



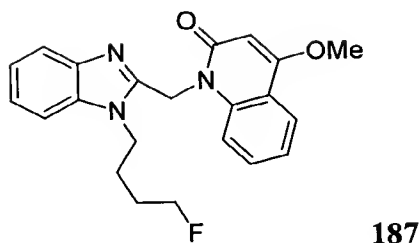
Compound **186** was prepared as described for the preparation of compound **25** using **186a** (538 mg, 2.40 mmol) and **159c**. The crude product **186** was obtained after precipitation from water. Recrystallization from ethyl acetate afforded 463 mg (45%) of **186** as an off-white solid.

¹H NMR (DMSO) δ 8.67 (s, 1 H), 7.80 (d, J = 7.8 Hz, 1H), 7.62 (m, 3H), 7.45 (d, J = 8.0 Hz, 1H), 7.32 (t, J = 7.8 Hz, 1H), 7.23 (t, J 8.0 Hz, 1H), 7.13 (t, J = 8.0 Hz, 1H), 5.86 (s, 2H), 4.51 (m, 4H), 1.82 (m, 4H); MS m/e 428 (M⁺).



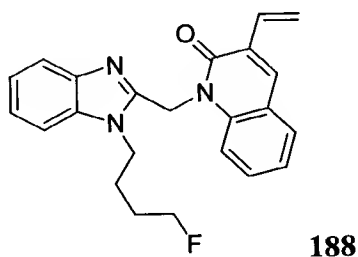
To a suspension of 2,4-dihydroxy quinoline (3.00 g, 18.6 mmol) and potassium carbonate (5.14 g, 37.2 mmol) in acetone (500 mL) was added dimethyl sulfate (2.1 mL, 22 mmol) and the resulting mixture heated at reflux during 5 hrs. The solvent was removed *in vacuo* and the residue triturated in water. The product was collected by filtration, washed with water and triturated from methanol to give 4-methoxy 2-quinolone **187a** (1.76 g, 54%) as a white solid, that had identical ¹H NMR data as reported (Reisch *et al.*, *Arch. Pharm.*, **1980**, 313, 751-755).

199



Compound **187** was prepared as described for compound **25** using **187a** (529 mg, 3.02 mmol) and **159c**. Compound **187** was purified by flash column chromatography (eluent 2% methanol in methylene chloride) to give 200 mg (17%) of **187** as an off-white solid.

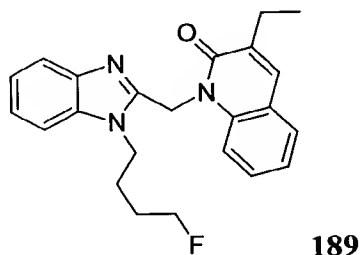
¹H NMR (DMSO) δ 7.93 (d, J = 7.5 Hz, 1H), 7.58 (m, 3H), 7.47 (d, J = 8.0 Hz, 1H), 7.25 (t, J = 7.3 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 7.13 (t, J = 7.4 Hz, 1H), 6.14 (s, 1H), 5.76 (s, 2H), 4.48 (m, 4H), 4.00 (s, 3H), 1.78 (m, 4H); MS m/e 380 (MH⁺).



A mixture of the bromide **186** (101 mg, 0.236 mmol), Pd(PPh₃)₄ (27 mg, 0.024 mmol), vinyl tri-*n*-butyltin (83 μL, 0.28 mmol) in toluene (1.2 mL) was heated at reflux for 1.5 hours under a nitrogen atmosphere. The mixture was cooled to room temperature, water and ethyl acetate (15 mL) were added and the layers separated. The organic phase was washed with water (2 x 10 mL), brine and dried with Na₂SO₄. The remaining yellow solid was washed with hexane and diethyl ether to give 100 mg product that was further purified by reverse phase preparative HPLC to give 40 mg (45%) of **188**.

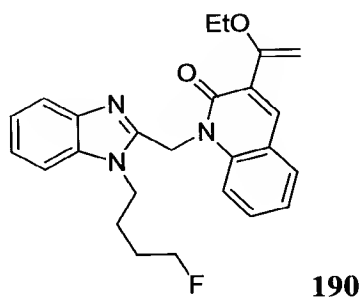
^1H NMR (CD_3OD) δ 8.12 (s, 1 H), 7.73 (d, J 7.9 Hz, 1 H), 7.50 (m, 4 H), 7.27 (m, 2 H), 7.18 (t, J 7.5 Hz, 1 H), 6.97 (dd, J 11.3, 17.7 Hz, 1 H), 6.14 (d, J 17.7 Hz, 1 H), 5.89 (s, 2 H), 5.42 (d, J 11.3, 1 H), 4.43 (m, 4 H), 1.80 (m, 4 H); MS m/e 376 (MH^+).

5



A mixture of the alkene **188** (21 mg, 0.056 mmol) and Pd-C (10%, 3 mg) in THF (1 mL) was stirred under a hydrogen atmosphere for 3 hours. The catalyst was filtered off and the filtrate concentrated to give compound **189** (21 mg, 100%) as a brownish solid.

^1H NMR (DMSO) δ 7.86 (s, 1H), 7.73 (d, J = 7.7 Hz, 1H), 7.60 (m, 2H), 7.48 (m, 2H), 7.23 (m, 2H), 7.13 (t, J = 7.7 Hz, 1 H), 5.82 (s, 2 H), 4.49 (m, 4H), 2.58 (q, J = 7.4 Hz, 2H), 1.77 (m, 4H), 1.21 (t, J = 7.4 Hz, 3H); MS m/e 378 (MH^+);

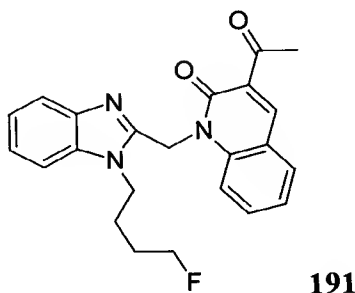


A mixture of the bromide **186** (51 mg, 0.119 mmol), $\text{Pd}(\text{PPh}_3)_4$ (14 mg, 0.012 mmol), ethoxyvinyl tri-*n*-butyltin (48 μL , 0.14 mmol) in toluene (1.2 mL) was heated at reflux for 2.5 hours under a nitrogen atmosphere. The mixture was

cooled to room temperature, water and ethyl acetate (15 mL) were added and the layers separated. The organic phase was washed with water (2 x 10 mL), brine and dried with Na₂SO₄. The remaining yellow solid was triturated from diethyl ether overnight to give compound **190** (34 mg, 68%) product.

5

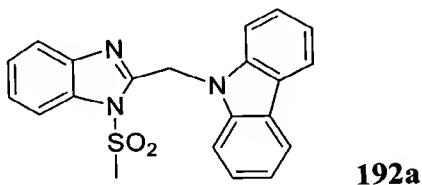
¹H NMR (DMSO) δ 8.33 (s, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.59 (m, 2H), 7.45 (d, J = 8.0 Hz, 1H), 7.30 (m, 2H), 7.22 (t, J = 7.3 Hz, 1H), 7.12 (t, J 7.3 Hz, 1H), 5.85 (s, 2H), 5.71 (s, 1H), 4.61 (s, 1H), 4.50 (m, 4H), 3.91 (q, J = 7.0 Hz, 2H), 1.80 (m, 4H), 1.39 (t, J = 7.0 Hz, 3H);

10 MS m/e 420 (MH⁺);

A solution of the vinyl ether **190** (12 mg, 0.029 mmol) in 1:1 1M HCl-THF (2 mL) was stirred at room temperature for 1 hour. The solvents were removed and the residue precipitated from diethyl ether to give 8 mg (70%) of **191** as an off-white solid.

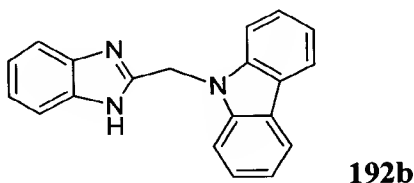
¹H NMR (DMSO) δ 8.65 (s, 1H), 8.07 (d, J = 7.7 Hz, 1H), 7.74 (t, J = 7.9 Hz, 1H), 7.68 (d, J = 8.6 Hz, 1H), 7.60 (m, 2H), 7.40 (m, 2H), 7.25 (t, J = 7.3 Hz, 1H), 6.02 (s, 2H), 5.71 (s, 1H), 4.54 (m, 2 H), 2.61 (s, 3H), 1.89 (m, 4H);

20 MS m/e 392 (MH⁺);



To a suspension of carbazole (226 mg, 1.35 mmol) in CH₃CN (8 mL) was added sodium hydride (60% suspension in mineral oil, 54 mg, 1.35 mmol). This mixture was stirred at room temperature for 30 minutes prior to addition of compound **1b** (500 mg, 1.45 mmol). After 3 hours, the reaction mixture was diluted with water and the orange solid was filtered. The solid was dissolved in CH₂Cl₂ and washed with brine solution. The organic layer was dried over MgSO₄ and evaporated. Flash column chromatography (3:1 hexanes/ EtOAc) gave 53 mg (10% yield) of compound **192a** :

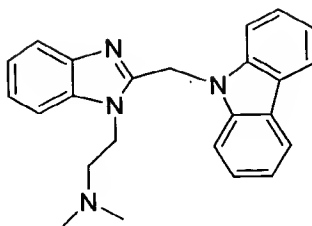
- ¹H NMR (CDCl₃) δ 2.58 (s, 3 H), 5.92 (s, 2 H), 7.17-7.21 (m, 4 H), 7.31-7.38 (m, 2 H), 7.51 (d, J = 8.3 Hz, 2 H), 7.72-7.79 (m, 2 H), 8.02 (d, J = 7.7 Hz, 2 H); IR (KBr, cm⁻¹) 3436, 2918, 1455, 1370, 1210, 1159, 1148, 744, 545; MS m/e 376 (MH⁺); Anal. Calcd for C₂₁H₁₇N₃O₂S • 0.25 H₂O: C, 66.38; H, 4.64; N, 11.06 Found: C, 66.49; H, 4.64; N, 10.81.



- Compound **192a** (166 mg, 0.44 mmol) was dissolved in CH₃OH / CH₂Cl₂ (20 mL, 1:1 ratio). Hydrazine (1.53 g, 47.78 mmol) was added and the reaction mixture was stirred at reflux for 48 hours. The solvent was evaporated to give a white residue which was triturated with water and then filtered to give 117 mg (89% yield) of compound **192b**:

- ¹H NMR (CD₃OD) δ 5.82 (s, 2 H), 7.16-7.25 (m, 4 H), 7.42 (td, J = 1.2, 7.1 Hz, 3 H), 7.52 (d, J = 8.2 Hz, 3 H), 8.12 (d, J = 7.6 Hz, 2 H); IR (KBr, cm⁻¹) 3049, 2642, 1625, 1460, 1326, 1210, 1034, 748, 722; MS m/e 298 (MH⁺); Anal. Calcd for C₂₀H₁₅N₃ • 0.40 H₂O: C, 78.87; H, 5.23; N, 13.80

Found: C, 78.88; H, 5.23; N, 13.44.

**192**

5 To compound **192b** (50 mg, 0.17 mmol) suspended in THF (5 mL) was added NaH (60% suspension in mineral oil, 20 mg, 0.50 mmol). After stirring at room temperature for 20 minutes, 2-chloro-N,N-dimethylethylamine hydrochloride (27 mg, 0.19 mmol) was added and the reaction mixture was stirred at 60 °C for 16 hours. The reaction was quenched with saturated aqueous
10 NaHCO₃ and was extracted with Et₂O. The combined organic extracts were dried over MgSO₄ and evaporated. Column chromatography (gradient hexanes/EtOAc, 1:1 to straight EtOAc) gave 29 mg (47% yield) of compound **192**:

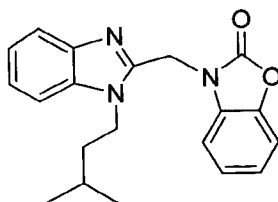
¹H NMR (CDCl₃) δ 1.77 (s, 6H), 1.80 (t, J = 7.5 Hz, 2H), 3.97 (t, J = 7.5 Hz, 2H),
15 5.83 (s, 2H), 7.24-7.31 (m, 5H), 7.41-7.46 (m, 2H), 7.58 (d, J = 8.2 Hz, 2H), 7.85 (d, J = 6.4 Hz, 1H), 8.10 (dd, J = 0.6, 7.2 Hz, 2H);

IR (KBr, cm⁻¹) 3413, 2933, 1597, 1485, 1461, 1323, 1258, 1209, 742, 718;

MS m/e 369 (MH⁺);

Anal. Calcd for C₂₄H₂₄N₄ • 0.70 H₂O : C, 75.64; H, 6.72; N, 14.70

20 Found: C, 75.87; H, 6.64; N, 14.32.

**193**

Compound **194** was prepared using the same procedure as compound **4** with compound **4c** and 2-benzoxazolinone:

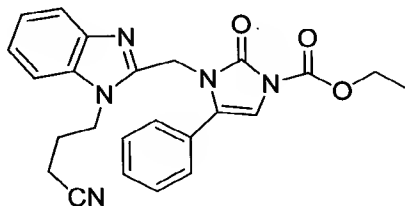
¹H NMR (CDCl₃) δ 0.98 (d, J = 6.6 Hz, 6H), 1.44-1.52 (m, 2H), 1.68-1.79 (m, 1H), 4.26-4.32 (m, 2H), 5.35 (s, 2H), 7.05-7.22 (m, 3H), 7.29- 7.35 (m, 3H), 7.38-7.41 (m, 1H), 7.79-7.82 (m, 1H);

IR (KBr, cm⁻¹): 2958, 1760, 1486, 1241, 1021, 755, 741;

MS m/e 336 (MH⁺);

Anal. Calcd for C₂₀H₂₁N₃O₂ • 0.25 H₂O: C, 70.67; H, 6.38; N, 12.36

Found: C, 70.89; H, 6.41; N, 12.30.

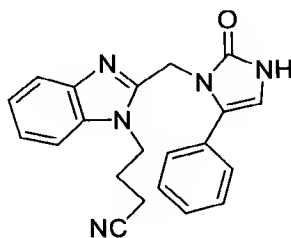


194

Compound **194** was prepared using the same procedure as compound **69** starting with compound **25b** and 3-ethoxycarbonyl-5-phenyl-imidazolone (Meanwell, N.A. et al, *J. Org. Chem.*, **1995**, 60, 1565-82).

¹H NMR (d₆-DMSO) δ 1.31 (t, J=7.0 Hz, 3H), 1.95-2.00 (m, 2H), 2.51-2.54 (m, 2H), 4.27-4.31 (m, 2H), 4.32-4.36 (m, 2H), 5.09 (s, 2H), 7.03 (d, J=6.8 Hz, 1H), 7.19-7.26 (m, 2H), 7.39-7.42 (m, 3H), 7.54-7.60 (m, 4H);

MS m/e 430 (MH⁺).

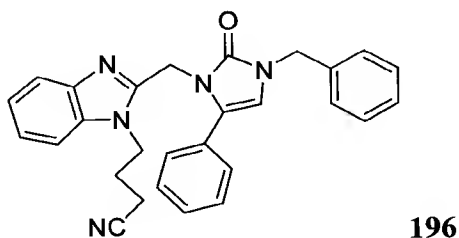


195

To a solution of **194** (62 mg, 0.14 mmol) in THF (1 mL) was added dimethylamine (2M in THF, 0.5 mL, 0.5 mmol) and stirred for 1 h. The product precipitated out the solution was collected by filtration to give 46 mg (89%) of **195** as a white solid.

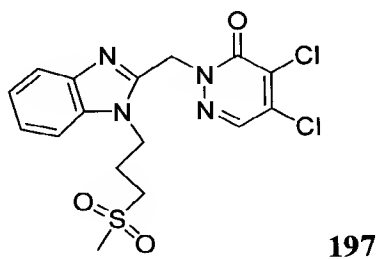
- 5 ^1H NMR (d_6 -DMSO) δ 1.99-2.02 (m, 2H), 2.56 (t, $J=7.4$ Hz, 2H), 4.32 (t, $J=7.4$ Hz, 2H), 5.07 (s, 2H), 6.65 (d, $J=2.4$ Hz, 1H), 7.16-7.19 (m, 1H), 7.22-7.30 (m, 2H), 7.34 (t, $J=7.4$ Hz, 2H), 7.50 (d, $J=7.2$ Hz, 2H), 7.56-7.58 (m, 2H), 10.38 (s, 1H);
MS m/e 358 (MH^+).

10



Compound **196** was prepared as described for compound **25**.

- 15 ^1H NMR (CDCl_3) δ 2.05-2.10 (m, 2H), 2.32 (t, $J=7.0$ Hz, 2H), 4.39 (t, $J=7.2$ Hz, 2H), 4.86 (s, 2H), 5.14 (s, 2H), 6.24 (d, $J=5.4$ Hz, 1H), 7.24-7.47 (m, 13H), 7.71 (d, $J=7.5$ Hz, 1H);
MS m/e 448 (MH^+).



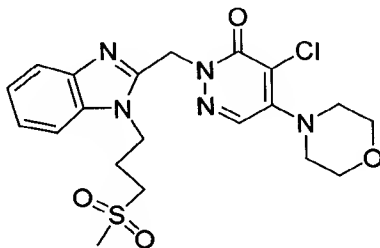
20

Compound **197** was prepared using the same procedure as compound **25** starting with compound **10d** and 4,5-dichloro-3-hydroxypyridazine.

^1H NMR (CDCl_3) δ 2.45-2.49 (m, 2H), 2.99 (s, 3H), 3.17 (t, $J=6.9$ Hz, 2H), 4.59 (t, $J=7.1$ Hz, 2H), 5.66 (s, 2H), 7.25-7.32 (m, 2H), 7.40 (d, $J=7.8$ Hz, 1H), 7.74 (d, $J=7.6$ Hz, 1H), 7.92 (s, 1H);

MS m/e 415 (MH^+);

- 5 Anal. Calcd for $\text{C}_{16}\text{H}_{16}\text{Cl}_2\text{N}_4\text{O}_3\text{S}$: C, 46.27; H, 3.88; N, 13.49. Found: C, 46.25; H, 3.90; N, 13.49.

**198**

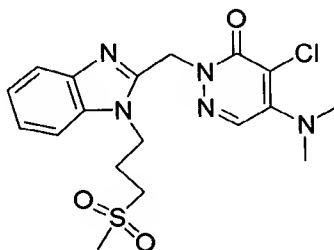
- 10 A solution of **197** (41 mg, 0.10 mmol) and morpholine (87 mg, 1.00 mmol) in ethanol (1 ml) was heated to reflux for 1 h. The solid formed after cooling was collected and washed by ethanol to give 31 mg (75%) of **198** as a white solid.

- 15 ^1H NMR (CDCl_3) δ 2.36-2.40 (m, 2H), 2.98 (s, 3H), 3.42-3.45 (m, 4H), 3.81-3.84 (m, 4H), 4.60 (t, $J=7.1$ Hz, 2H), 5.67 (s, 2H), 7.27-7.33 (m, 2H), 7.41 (d, $J=7.7$ Hz, 1H), 7.74 (s, 1H), 7.80 (d, $J=7.7$ Hz, 1H);

MS m/e 466 (MH^+);

Anal. Calcd for $\text{C}_{20}\text{H}_{24}\text{ClN}_5\text{O}_4\text{S}$: C, 51.55; H, 5.19; N, 13.03. Found: C, 51.35; H,

- 20 5.05; N, 14.86.

**199**

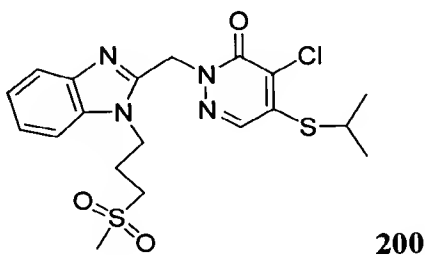
A solution of **197** (41 mg, 0.10 mmol) and dimethylamine (40% aq, 0.2 ml) in ethanol (1 ml) was heated to 120°C in a sealed tube for 1 h. The solvent was removed and the residue purified by reverse phase preparative HPLC (gradient, 10% MeOH in H₂O with 0.1% TFA to 90% MeOH in H₂O with 0.1% TFA) to give 29 mg (68%) of **199**.

¹H NMR (CDCl₃) δ 2.33-2.38 (m, 2H), 2.97 (s, 3H), 3.14-3.17 (m, 8H), 4.58 (t, J=7.1 Hz, 2H), 5.63 (s, 2H), 7.27-7.32 (m, 2H), 7.39 (d, J=7.7 Hz, 1H), 7.72 (s, 1H), 7.78 (d, J=7.7 Hz, 1H);

MS m/e 424 (MH⁺);

Anal. Calcd for C₁₈H₂₂ClN₅O₃S: C, 50.99; H, 5.23; N, 16.52;

Found: C, 50.91; H, 4.97; N, 16.37.



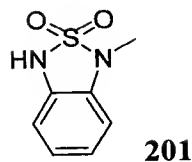
15

A solution of **197** (41 mg, 0.10 mmol), 2-propanethiol (76 mg, 1.00 mmol) and TEA (20 mg, 0.20 mmol) in ethanol (1 ml) was heated to reflux for 1 h. The solvent was removed and the residue purified by reverse phase preparative HPLC (gradient, 10% MeOH in H₂O with 0.1% TFA to 90% MeOH in H₂O with 0.1% TFA) to give 26 mg (57%) of **200**.

¹H NMR (CDCl₃) δ 1.44 (d, J=6.6 Hz, 6H), 2.39-2.44 (m, 2H), 2.97 (s, 3H), 3.16 (t, J=7.0 Hz, 2H), 3.64-3.69 (m, 1H), 4.58 (t, J=7.1 Hz, 2H), 5.63 (s, 2H), 7.24-7.31 (m, 2H), 7.39 (d, J=7.8 Hz, 1H), 7.75 (d, J=7.8 Hz, 1H), 7.81 (s, 1H);

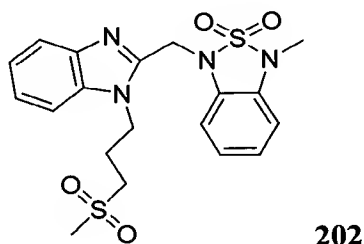
MS m/e 455 (MH⁺).

208



A solution of N-methyl-1,2-phenylenediamine (2.44 g, 20.0 mmol) and sulfamide (2.11 g, 22.0 mmol) in diglyme (20 mL) was heated to reflux for 1 h.

- 5 The solvent was removed and the residue taken up in EtOAc (300 ml) and washed with 1N HCl then saturated sodium chloride. The organic layer was dried over MgSO₄ and evaporated to give 3.680 g (99%) of **201** as a red viscous oil. The crude product was used for the next reaction without further purification.

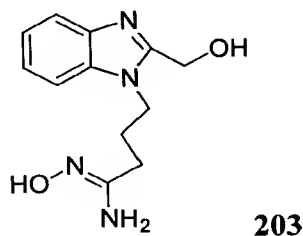


10

Compound **202** was prepared using the same procedure as Compound **25** starting with Compound **10d** and **201**.

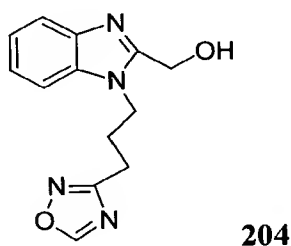
- 15 ¹H NMR (CDCl₃) δ 2.23-2.30 (m, 2H), 2.80 (s, 3H), 3.09 (t, J=7.5 Hz, 2H), 3.50 (s, 3H), 4.52 (t, J=8.0 Hz, 2H), 5.13 (s, 2H), 6.76 (d, J= 7.7 Hz, 1H), 6.93 (t, J=7.7 Hz, 1H), 7.02 (t, J=7.6 Hz, 1H), 7.23 (d, J=7.8 Hz, 1H), 7.32-7.44 (m, 2H), 7.44-7.46 (m, 1H), 7.82-7.84 (m, 1H); MS m/e 435 (MH⁺).

N-Hydroxy-4-(2-hydroxymethyl-benzoimidazol-1-yl)-butyramidine



- 5 A mixture containing 4-(2-hydroxymethyl-benzoimidazol-1-yl)-butyronitrile, **25a**, (40.0 g, 186 mmol), hydroxylamine hydrochloride (46.5 g, 0.689 mole) and potassium carbonate (51.4 g, 0.372 mole) in ethanol (400 mL) and water (200 mL) was heated at 80°C and stirred overnight. The solvents were removed *in vacuo* and water was added. The white precipitate was collected by filtration,
- 10 washed with water and dried *in vacuo* to afford N-hydroxy-4-(2-hydroxymethyl-benzoimidazol-1-yl)-butyramidine (35.8 g, 78%) as a white solid:
- ¹H NMR (DMSO) δ 1.97-2.06 (m, 4H), 4.27 (t, 2H, J = 7.4 Hz), 4.72 (s, 2H), 5.44 (br s, 2H), 5.64 (br s, 1H), 7.18 (t, 1H, J = 7.5 Hz), 7.23 (t, 1H, J = 7.5 Hz), 7.57 (d, 1H, J = 7.5 Hz), 7.59 (d, 1H, J = 7.5 Hz), 8.83 (s, 1H);
- 15 MS m/e 249 (MH⁺);

[1-(3-[1,2,4]Oxadiazol-3-yl-propyl)-1H-benzoimidazol-2-yl]-methanol



20

A suspension of N-hydroxy-4-(2-hydroxymethyl-benzoimidazol-1-yl)-butyramidine, **203**, (500 mg, 2.01 mmol) in trimethyl orthoformate (5 mL) in the presence of BF₃·OEt₂ (50 μL) in a sealed tube was placed in a microwave oven (Smith Creator, Personal Chemistry) and heated at 100°C for 15 min while

stirring, resulting in the dissolution of all the material. The reaction was repeated 5 times. The 6 batches were combined and concentrated *in vacuo*. The residue was treated with 1M HCl (15 mL) and THF (15 mL) and left overnight.

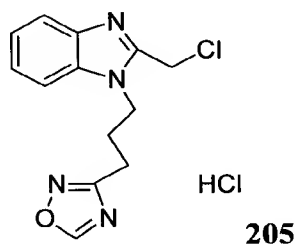
Concentration followed by trituration from dichloromethane and recrystallization

5 from isopropyl alcohol and methanol afforded [1-(3-[1,2,4]oxadiazol-3-yl-propyl)-1H-benzoimidazol-2-yl]-methanol (2.28 g, 73%) as a white solid:

^1H NMR (DMSO) δ 2.27 (quint, 2H, J 7.4 Hz), 2.95 (t, 2H, J = 7.5 Hz), 4.52 (t, 2H, J = 7.6 Hz), 5.06 (s, 2H), 6.65 (br s, 1H), 7.57 (t, 1H, J = 7.5 Hz), 7.60 (t, 1H, J = 7.3 Hz), 7.79 (d, 1H, J = 7.8 Hz), 8.01 (d, 1H, J = 7.6 Hz), 9.54 (s, 1H);

10 MS m/e 259 (MH^+);

2-Chloromethyl-1-(3-[1,2,4]oxadiazol-3-yl-propyl)-1H-benzoimidazole, HCl salt



15

To a cooled (0°C) suspension of [1-(3-[1,2,4]oxadiazol-3-yl-propyl)-1H-benzoimidazol-2-yl]-methanol, **204**, (850 mg, 3.29 mmol) in dichloro methane (20 mL) was added thionyl chloride (360 μL , 4.94 mmol). The solution was stirred at 0°C for 15 min. and then for 1.5 h at ambient temperature. The solution was

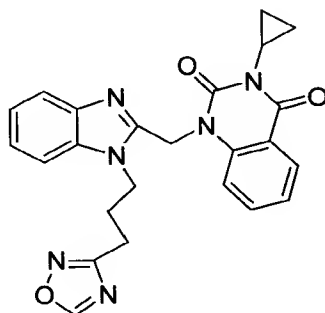
20 concentrated *in vacuo* to give 2-chloromethyl-1-(3-[1,2,4]oxadiazol-3-yl-propyl)-1H-benzoimidazole, HCl salt as a white solid in quantitative yield, which was used without further purification:

^1H NMR (DMSO) δ 2.27 (quint, 2H, J = 7.5 Hz), 2.95 (t, 2H, J = 7.5 Hz), 4.55 (t, 2H, J = 7.1 Hz), 5.27 (s, 2H), 7.46 – 7.53 (m, 2H), 7.78 (d, 1H, J = 7.9 Hz), 7.89 (d, 1H, J = 7.9 Hz), 9.55 (s, 1H);

25

MS m/e 277 (MH^+);

3-Cyclopropyl-1-[1-(3-[1,2,4]oxadiazol-3-yl-propyl)-1H-benzoimidazol-2-ylmethyl]-1H-quinazoline-2,4-dione



206

5

To a solution of 3-cyclopropyl-1H-quinazoline-2,4-dione, **159a**, (83 mg, 0.41 mmol) in DMF (6 mL) was added BTPP (269 mg, 0.86 mmol) and the solution was stirred for 15 min. 2-Chloromethyl-1-(3-[1,2,4]oxadiazol-3-yl-propyl)-1H-benzoimidazole, **205**, HCl salt (128 mg, 0.41 mmol) was added and stirring was

10

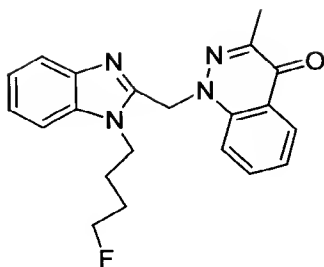
continued for 1 h. The solution was concentrated and water was added to the residue. The white precipitate was collected by filtration, washed with water and purified by flash chromatography (eluent dichloromethane – ethyl acetate 2:1, 1:1) to afford 3-cyclopropyl-1-[1-(3-[1,2,4]oxadiazol-3-yl-propyl)-1H-benzoimidazol-2-ylmethyl]-1H-quinazoline-2,4-dione (26 mg, 14%) as a white

15

solid:
 ^1H NMR (DMSO- d_6) δ 0.72 – 0.75 (m, 2H), 1.02 – 1.06 (m, 2H), 2.26 (quint, 2H, $J = 7.4$ Hz), 2.74 – 2.78 (m, 1H), 2.95 (t, 2H, $J = 7.4$ Hz), 4.49 (t, 2H, $J = 7.4$ Hz), 5.64 (s, 2H), 7.14 (t, 1H, $J = 7.6$ Hz), 7.24 (t, 1H, $J = 7.6$ Hz), 7.28 (t, 1H, $J = 7.5$ Hz), 7.49 (t, 1H, $J = 8.0$ Hz), 7.51 (d, 1H, $J = 8.5$ Hz), 7.62 (d, 1H, $J = 8.1$ Hz), 7.68 (t, 1H, $J = 7.9$ Hz), 8.07 (d, 1H, $J = 7.9$ Hz), 9.55 (s, 1H);
MS m/e 443 (MH^+);

20

212

**207**

To a solution of 3-methyl-1H-cinnolin-4-one (200 mg, 1.25 mmol) (prepared as described by B. Singh, *J. Het. Chem.* **1991**, 881-883) in THF (2 ml) was added

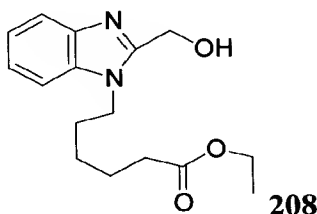
5 BTTP (1.15 ml, 3.75 mmol) and the mixture stirred for 15 minutes at 23°C.

Compound **159c** was added and the mixture stirred for 12 h. The solvent is removed and the residue triturated with water. A tan solid was isolated by filtration. The solid is further purified by column chromatography (50% EtOAc in hexanes) as elutant to give 170 mg (37%) of **207**.

10

¹H NMR (DMSO-d₆) δ : 1.68-1.77 (m, 4H), 2.30 (s, 3H), 4.40-4.42 (m, 3H), 4.50-4.52 (m, 1H), 6.04 (s, 2H), 7.16 (t, J = 7.6 Hz, 1H), 7.25 (t, J = 7.7 Hz, 1H), 7.44 (t, J = 7.2 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.78 (t, 7.4 Hz, 1H), 7.90 (d, J = 8.9 Hz, 1H), 8.14 (d, J = 8.1 Hz, 1H);

15 MS m/e 364 (MH⁺).

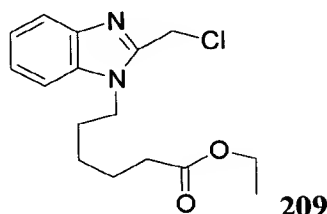
**208**

Compound **208** was prepared as described for compound **25**, using 2-
20 hydroxymethylbenzimidazole and ethyl 6-bromohexanoate.

213

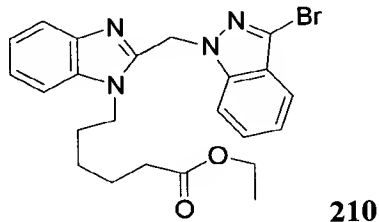
^1H NMR (CD_3OD) δ 1.18-1.22 (m, 3 H), 1.42-1.45 (m, 2 H), 1.66-1.69 (m, 2 H), 1.90-1.92 (m, 2 H), 2.30-2.33 (m, 2 H), 4.06-4.10 (m, 2 H), 4.35-4.38 (m, 2 H), 4.89 (s, 2 H), 7.23-7.32 (m, 2 H), 7.51-7.53 (m, 1 H), 7.60-7.63 (m, 1 H); MS m/e 291 (MH^+).

5



Compound **209** was prepared as described for compound **4c**.

^1H NMR (CD_3OD) δ 1.21 (t, $J=7.1$ Hz, 3H), 1.47-1.54 (m, 4H), 1.65-1.74 (m, 2H), 1.95-2.05 (m, 2H), 2.34 (t, $J=7.2$ Hz, 2H), 4.03-4.12 (m, 2H), 4.58 (t, $J=7.7$ Hz, 2H), 5.31 (s, 2H), 7.68-7.72 (m, 2H), 7.83-7.85 (m, 1H), 7.97-8.00 (m, 1H); MS m/e 309 (MH^+).



15

Compound **210** was prepared as described for compound **25** using compound **4a**.

^1H NMR (CD_3OD) δ 1.18-1.32 (m, 5H), 1.46-1.61 (m, 4H), 2.21 (t, $J = 7.3$ Hz, 2H), 4.04-4.11 (m, 2H), 4.49 (t, $J = 7.8$ Hz, 2 H), 6.20 (s, 2H), 7.33-7.37 (m, 1H), 7.54-7.60 (m, 3H), 7.64-7.68 (m, 1H), 7.73-7.83 (m, 3H);

20 MS m/e 469, 471 (MH^+).

BIOLOGICAL ACTIVITY

The antiviral activity of these compounds against respiratory syncytial virus was determined in HEp-2 (ATCC CCL 23) cells that were seeded in 96 well microtiter plates at 1.5×10^4 cells/100 μ L/well in DMEM (Dulbecco's Modified Eagle's Medium) supplemented with penicillin, streptomycin, glutamine, and 10% fetal bovine serum. The cells were incubated overnight at 37 °C, the culture medium was removed, and cells were infected (100 μ L volume in medium containing 2% fetal bovine serum) with respiratory syncytial virus Long strain at 5000 plaque forming units/mL. The compounds, 100 μ L at appropriate dilution, were added to the cells 1 hour post infection. After incubation for 4 days at 37 °C, the plates were stained with MTT solution (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) and incubated for 4 hours at 37 °C. The media was aspirated from the cells and 100 μ L/well of acidified isopropanol (per liter: 900 mL isopropanol, 100 mL Triton X100, and 4 mL conc. HCl) was added. Plates were incubated for 15 minutes at room temperature with shaking, and an optical density (OD 540) reading at 540 nanometer (nm) was obtained. The optical density reading is proportional to the number of viable cells. The increase in the number of viable cells reflects the protective, antiviral activity of the compound. Assays comparing MTT staining in uninfected cells containing compound with uninfected cells in the absence of compound provide a measure of cellular toxicity. The control compound in this assay is Ribavirin which exhibits 100% cell protection at 2.5 μ g/mL (corresponding to 10.2 μ M).

The antiviral activity of compounds, designated as EC_{50} , is presented as a concentration that produces 50% cell protection in the assay. The compounds disclosed in this application show antiviral activity with EC_{50} 's between 50 μ M and 0.001 μ M. Ribavirin has an EC_{50} of 3 μ M in this assay.